The Coordination of Breathing and Swallowing Across the Human Lifespan: Implications for Neural Control

By

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Preface

This PhD thesis conforms to the referencing style recommended by the American Psychological Association Publication Manual (5th ed.) and spelling recommended by the New Oxford Dictionary for Writers and Editors (2005).

The research was carried out between April 2003 and March 2005 primarily at the Van der Veer Institute for Parkinson's and Brain Research, Christchurch, New Zealand. The research was supervised by Dr Maggie-Lee Huckabee, University of Canterbury, and Associate Professor Richard Jones, Christchurch School of Medicine and Health Sciences. Financial support was provided by the Top Achievers Doctoral Scholarship from the Foundation for Research, Science, and Technology (now from the Tertiary Education Commission). This research is a continuation of the pilot study conducted in 2001-2002 in which Dr Maggie-Lee Huckabee, Miss Nicola Friend (summer student), and I (research assistant) were involved. The results of this pilot study are in press (Kelly, B.N., Huckabee, M.L. & Friend, N. The coordination of respiration and swallowing for volitional and reflexive swallows - a pilot study. *Journal of Medical Speech Pathology*).

Preliminary results from the PhD research have been presented at the following local and international conferences:

Dysphagia Research Society annual meetings (Montreal, Canada, 2004 and Scottsdale, AZ, U.S.A., 2006);

New Zealand Speech-language Therapists' Association Conference (Christchurch, New Zealand, 2006);

Canterbury Health Research Conference (Christchurch, New Zealand, 2005; awarded joint prize for best student presentation);

Canterbury Conference on Communication Disorders (Christchurch, New Zealand, 2005; awarded the Medical Staffing International-New Zealand Speech-Language Therapists' Association Doctoral Award);

Introduction to Therapy in Acute Paediatrics (Auckland, New Zealand, 2004; invited presentations);

22nd International Australasian Winter Conference on Brain Research (Queenstown, New Zealand, 2004; awarded the Goddard prize for best student presentation).

The following publications have also been generated from this research:

Kelly, B.N., Huckabee, M.L., Jones, R.D. & Frampton, C.M.A. (in press). Nutritive and non-nutritive swallowing apnoea duration in term infants: implications for neural control mechanisms. *Respiratory Physiology and Neurobiology*.

Kelly, B.N., Huckabee, M.L., Jones, R.D. & Frampton, C.M.A. (provisionally accepted). The first year of human life: coordinating respiration and nutritive swallowing. *Dysphagia*.

Kelly, B.N., Huckabee, M.L., Jones, R.D. & Frampton, C.M.A. (in press). Coordinating respiration and nutritive swallowing in the first year of life [Abstract]. *Dysphagia*.

Kelly, B.N., Huckabee, M.L., Jones, R.D. & Frampton, C.M.A. (2006). Coordinating respiration and nutritive swallowing in the first year of life [Abstract]. *New Zealand Medical Journal, 119(1213).* Abstract retrieved from http://www.nzma.org.nz/journal/119-1231/1922/.

Kelly, B.N., Huckabee, M.L., Jones, R.D. & Frampton, C.M.A. (2005). The maturation of the coordination of infantile breathing and non-nutritive swallowing [Abstract]. *Dysphagia, 20,* 68-86.

Kelly, B.N., Huckabee, M.L., Jones, R.D. & Frampton, C.M.A. (2004). Cortical influence over infantile breathing-swallowing coordination [Abstract]. *Proceedings of the 22nd Australasian Winter Conference on Brain Research.* Abstract retrieved from http://psy.otago.ac.nz/awcbr/Abstracts2004.htm#Kelly, 34.

Abstract

Our understanding of the neural control of breathing-swallowing coordination (BSC) is largely unclear. Although brainstem control is undoubtedly predominant, this research investigated the hypothesis that the cortex becomes increasingly influential in BSC between birth and adulthood. The main paradigm used to test this primary hypothesis was a comparison of BSC in conditions along a continuum of volitional through non-volitional swallowing on the basis of a decreasing level of cortical activation along this continuum. Voluntarily-initiated swallows during wakefulness were at one end of the continuum and reflexively-initiated swallows during sleep were at the other extreme. Non-volitional wakeful swallows were considered between these two conditions.

The BSC of ten infants between birth and 1 year of age and twenty adults between the ages of 20 and 75 years was recorded using non-invasive time-locked recording methods. In order to apply the 'continuum-of-volition' paradigm to swallowing conditions in infants, BSC was monitored during nutritive (breast- or bottle-feeding), non-nutritive wake, and sleep swallows. Infants were monitored longitudinally to determine whether maturation of the cortex and corticobulbar tracts during the first year of life influenced the patterns of BSC. In adults, BSC was monitored during three non-nutritive conditions: volitional, spontaneous wake, and sleep conditions.

Post-swallow expiration was found to be predominant in all conditions for all participants at all ages. In addition, the infant results revealed that nutritive BSC matured during the first year of life and differed to non-nutritive wakeful BSC, particularly in the first 2 months of life. Non-nutritive wakeful and sleep BSC did not differ from one another. In summary, the infant results support increasing cortical input into volitional nutritive BSC, an early impact of feeding on BSC, and no difference between BSC when asleep and non-volitional non-nutritive swallows when awake. The results obtained from adults revealed that irrespective of the level of arousal, volitional BSC is different to non-volitional BSC. These results imply that cortical influence on BSC is limited to conditions in which swallowing is voluntarily initiated.

The combined interpretation of infant and adult results suggest that cortical influence over BSC, although increasing with maturation, is limited to the volitional swallowing conditions of feeding in infants and during non-nutritive but volitional swallows in adults. From this, it can be deduced that the most likely cortical sites involved in BSC are those involved in the voluntary initiation or planning of swallowing.

Infant and adult swallowing apnoea duration (SAD) was also compared across all of the above conditions. SAD was influenced by feeding throughout the first year of life but was not influenced by level of arousal at any stage in the first year or in adulthood. Also, SAD did not change with age in any swallowing condition during infancy. However, comparison of non-nutritive wake SAD across the lifespan revealed that SAD of newborns and young adults is shorter than that of elderly adults, with no difference between consecutive age-groups: newborns, one-year-olds, and young adults. These results suggest SAD is largely mature at birth and impervious to descending suprabulbar influence.

Finally, the effects of volitional swallowing and level of arousal on peak submental surface electromyography (SEMG) was investigated in adults. Like BSC, submental muscle activity was influenced only by volitional swallowing, being longer for volitional than non-volitional swallows without being influenced by level of arousal. Since peak submental SEMG activity represents a measure of relative hyolaryngeal excursion, these results suggest that the cortex has some degree of influence over this particular feature of pharyngeal-stage swallowing.

Acknowledgements

My academic supervisors, Dr Maggie-Lee Huckabee and Assoc. Prof. Richard Jones, have not only made substantial contributions to this thesis but have also enriched my entire postgraduate experience. It was Maggie-Lee's passion for the subject area that inspired me to engage in swallowing research. Although there are many things for which I am indebted to her, she has contributed considerably to my academic development, especially in encouraging me to always aim high, and guiding me in the art of writing succinct prose. Richard, for whom this area of research is largely novel, has fuelled my general interest in research through his consistently positive, inquisitive, and methodical approach to problem-solving. His sense of humour, sound advice, and unfailing support made this journey a smoother and more enjoyable one. I wish to express sincere gratitude to them both for their guidance throughout the past 3 years.

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I am most grateful for the invaluable statistical advice provided by Assoc. Prof. Christopher Frampton of the Department of Medicine, Christchurch School of Medicine and Health Sciences. I also wish to thank the interraters: Grant Carroll, Elizabeth Haughey, Li Pyn Leow, Inn Sze Low, and Lesley Thorndycraft for the many hours of tedious work they so willingly and voluntarily contributed. Lauren Ragg played a large role in infant participant recruitment, data collection and analysis. Kerrie Gallagher, Andrea Hofmayer, and Noreen Kelly also assisted occasionally in data collection. Sharon Broadmore, Elizabeth Haughey, and Li Pyn Leow gave up many nights to assist me in conducting the overnight sleep studies. Despite sleep deprivation and dealing with their own workloads, their helpfulness and companionship remained steadfast.

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Abbreviations

BSC	breathing-swallowing coordination
CNS	central nervous system
CP	cerebral palsy
CPG	central pattern generator
DDST II	Denver Developmental Screening Test II
EE	expiration-SA-expiration
EEG	electroencephalography
EI	expiration-SA-inspiration
fMRI	functional magnetic resonance imaging
IE	inspiration-SA-expiration
II	inspiration-SA-inspiration
LCR	laryngeal chemoreflex
LH	lateral hypothalamus
LSD test	least significant difference test (Fisher's)
M	mean
MRI	magnetic resonance imaging
NA	nucleus ambiguus
NREM	non-rapid eye movement
NTS	nucleus tractus solitarius
P	mid-pause
PET	positron emission tomography
PNS	peripheral nervous system
REM	rapid eye movement
SA	swallowing apnoea
SAD	swallowing apnoea duration
SD	standard deviation
SE	standard error
SEMG	surface electromyography
SIDS	sudden infant death syndrome
SLN	superior laryngeal nerve
SMA	supplementary motor area
UOS	upper oesophageal sphincter

PART I: INTRODUCTION AND LITERATURE REVIEW

Chapter 1. Introduction

This research provides insight into the neural controls of breathing-swallow coordination (BSC) in healthy humans across the lifespan.

The oropharynx is a conduit for both swallowing and respiration. Thus, infant and adult breathing is momentarily halted during nutritive and non-nutritive swallowing (Hiss, Treole, & Stuart, 2001; Koenig, Davies, & Thach, 1990; Martin-Harris, Brodsky, Michel, & Walters, 2003; Miller & DiFiore, 1995; Wilson, Thach, Brouillette, & Abu-Osba, 1981) in order to prevent the swallowed bolus from entering the airway (aspiration). This cessation in respiration is known as deglutition apnoea or swallowing apnoea (SA). BSC is typically described by the proportional distribution of the respiratory phases that occur before and after SA or swallowing.

In healthy infants, SA can occur in all of the following five respiratory-phase categories: inspiration-SA-inspiration (II), inspiration-SA-expiration (IE), expiration-SA-expiration (EE), expiration-SA-inspiration (EI), and during benign prolonged respiratory pauses (P). These prolonged pauses last between 2 s (Curzi-Dascalova & Christova-Gueorguieva, 1983; Curzi-Dascalova, Christova-Gueorguieva, Lebrun, & Firtion, 1984; Hoppenbrouwers, Hodgman, Arakawa, Harper, & Sterman, 1980) and 15 s (Hoppenbrouwers et al., 1977). Healthy adults do not exhibit prolonged respiratory pauses under normal swallowing conditions, so SA may occur in any of the II, IE, EE, or EI categories.

The neural substrates responsible for BSC aren't entirely clear. It is well documented that the brainstem exerts significant influence over breathing and swallowing (Horn & Waldrop, 1998; Miller, 1999; Mrini & Jean, 1995; Sawczuk & Mosier, 2001; Smith, Ellenberger, Ballanyi, Richter, & Feldman, 1991) and the coordination of breathing and swallowing (Bianchi, Denavit-Saubie, & Champagnat, 1995; Feroah, Forster, Fuentes, Wenninger et al., 2002; Gestreau, Grelot, & Bianchi, 2000; Gestreau, Milano, Bianchi, & Grelot, 1996; Hayashi & McCrimmon, 1996; Larson, Yajima, & Ko, 1994; Oku, Dick, & Cherniack, 1993; Oku, Tanaka, & Ezure, 1994; Saito, Ezure, & Tanaka, 2002; Saito, Ezure, Tanaka, & Osawa, 2003). There is also an abundance of evidence that multiple cortical sites are involved in breathing and swallowing, particularly under volitional conditions, although the exact nature

of the influence of these sites is uncertain (Colebatch et al., 1991; Daniels & Foundas, 1997; Davenport & Reep, 1995; Evans, Shea, & Saykin, 1999; Fink et al., 1996; Hamdy, Mikulis et al., 1999; Hamdy, Rothwell et al., 1999; Harris et al., 2005; Horn & Waldrop, 1998; Huckabee, Deecke, Cannito, Gould, & Mayr, 2003; Kern, Birn et al., 2001; Kern, Jaradeh, Arndorfer, & Shaker, 2001; Lefaucheur & Lofaso, 2002; Miller & Bowman, 1977; Mosier & Bereznaya, 2001; Mosier et al., 1999; Moss, 2005; Murphy, Mier, Adams, & Guz, 1990; Satow et al., 2004; Sumi, 1969, 1972; Toogood et al., 2005; Zald & Pardo, 1999). It can be argued that swallowing-related sites may not only represent swallowing but also respiratory events. For example, the supplementary motor area (SMA) is thought to be involved in the preparation of volitional swallowing (Huckabee et al., 2003) but it may also be involved in planning the respiratory phase that occurs before and after it, that is, BSC. This is supported by emerging evidence that suggests that cortical input may too influence BSC (Kelly, Huckabee, & Friend, in press; Nishino & Hiraga, 1991).

The typical pattern of BSC in awake humans is during expiration (EE) (Hiss et al., 2001; Klahn & Perlman, 1999; Martin, Logemann, Shaker, & Dodds, 1994; McFarland & Lund, 1995; Perlman, Ettema, & Barkmeier, 2000; Preiksaitis, Mayrand, Robins, & Diamant, 1992), but when cortical input is minimized, as in the unconscious state of anaesthetized patients or during natural sleep, an increased variability in this coordination is observed (Kelly et al., in press; Nishino & Hiraga, 1991). Greater variability during these conditions compared to wakefulness suggests that heightened cortical activity associated with increased arousal may have a significant influence over BSC (Kelly et al., in press). However, given the methodological approaches adopted by prior research (discussed in the more comprehensive literature review that follows), the presence of cortical input remains speculative.

This research improved upon the methodologies used previously (Kelly et al., in press; Nishino & Hiraga, 1991) to clarify whether cortical influences play a role in determining the pattern of BSC. This research primarily involved the monitoring of BSC during swallowing tasks that varied in terms of the degree of cortical activity: at one extreme, volitional non-nutritive swallows during wakefulness in adults (heightened cortical activation) and, at the other extreme, non-volitional swallows performed during non-rapid-eye-movement (NREM) sleep (minimized cortical activation) in adults.

During sleep, particularly NREM sleep, cortical activity is markedly reduced compared to wakefulness in adults (Hobson & Pace-Schott, 2002). During NREM sleep, respiration is

under fully automated control, whereas during wakefulness, cortical excitation and supramedullary regions can override this automated control (Moss, 2005). It is presumed that the same applies to the automated control of swallowing. Using the sleep-wake paradigm, truly volitional and non-volitional swallowing conditions can be compared. The comparison of volitional and non-volitional/reflexive swallowing is thought to be a valid approach to determining the nature of cortical input in swallowing, and, hence, possibly BSC as well. "Since there is no volitional input for initiation of a reflexive swallow, comparison of its cortical representation with that of volitional swallow can provide a study model that can potentially increase our understanding of the non-sensory/motor cortical control of swallowing" (Kern, Jaradeh et al., 2001, p. 354). In addition to the non-volitional sleep and volitional wake swallowing conditions, BSC under a *spontaneous* wake swallowing condition was also recorded. The aim was to specifically address the impact of level of arousal[1] on BSC.

To further elucidate cortical control, the BSC of human neonates[2] was monitored under similar conditions. Given the behavioural difficulty in eliciting non-nutritive volitional swallows from neonates, BSC during breast- or bottle-feeding was monitored. Non-nutritive swallowing during wakefulness and sleep was also monitored. In doing so, normative BSC patterns during sleep, wake, and feeding were determined, prior to the completion of postnatal myelination of the corticobulbar tract (Sarnat, 1989) and cortical development (Gibson, 1991). The same three conditions were monitored repeatedly throughout the first year of life, with the aim of detecting maturation patterns in BSC that are associated with normal development. It was hypothesized that BSC during wake would become increasingly differentiated from the sleep pattern of BSC as the infants matured and descending cortical influence increased. There appears to be no published data comparing BSC under sleep and wake non-nutritive swallowing conditions in healthy term infants[3]. Moreover, only evidence of the maturation of BSC during nutritive swallowing has been documented but this is limited to preterm (premature) neonates and term neonates under 1 month of age (Lau, Smith, & Schanler, 2003; Mizuno & Ueda, 2003).

[1] 'Level of arousal' refers to the electrophysiological state of the brain (reviews by Sarter, Givens, & Bruno, 2001, and Tassi & Muzet, 2001) in contrast to 'level of consciousness' which implies "awareness and the building up of mental representations" or 'level of alertness' which "would reflect the subjective feeling of well-being related to the level of arousal" (review by Tassi & Muzet, 2001, p. 188).
[2] A child less than one month of age is considered a neonate or newborn (Pugh, 2000).
[3] A child under the age of 12 months is considered an infant (Pugh, 2000).

The postnatal development of supramedullary structures is thought to be responsible for the maturation of feeding behaviour; at birth, feeding is largely reflexive and involves higher central nervous system (CNS) structures to a greater degree only later in infancy (Stevenson & Allaire, 1991). Furthermore, patterns of myelination coincide with developmental feeding milestones in the first year of life. For example, postnatal myelination of important swallow-related sites and the emergence of voluntary feeding behaviours coincide (review by Rogers & Arvedson, 2005). Hence, the maturation of BSC during feeding may reflect these developmental processes, particularly increasing input of suprabulbar mechanisms.

It is recognized, however, that the maturation of the brainstem neural networks (central pattern generators) may account for postnatal changes in mammalian infant BSC (Miller, 1999). Unfortunately, in humans it is difficult to separate bulbar (brainstem) from suprabulbar (all structures above the brainstem) maturation using non-invasive techniques. Thus, behavioural experimental research comparing conditions in which the degree of cortical activation can be controlled is a reasonable approach to determining the presence of suprabulbar influences. Moreover, the use of neural imaging techniques to identify the sites responsible for BSC is not feasible due to the tight temporal sequencing of the biomechanics of BSC. For instance, SA occurs 442 ± 1285 ms before the onset of a pharyngeal swallow (Martin-Harris et al., 2003) and, therefore, it would be difficult to distinguish between the neural controls for swallowing and those for respiratory cessation.

In the chapters that follow the literature review (Chapter 2), data obtained from healthy term neonates and infants (Part II) and data obtained from healthy young and elderly adults (Part III) are presented. Where appropriate, comparisons between the age groups are also made (Part IV) to provide normative data on the maturation of BSC. The maturational patterns are interpreted in reference to the evidence provided by adults and in the light of global brain development to assist in the identification of potential influential suprabulbar sites. The broad implications for the neural controls of BSC and implications for certain pathologies such as sudden infant death syndrome (SIDS) are also discussed.

Chapter 2. Literature Review

2.1 The Importance of Coordinated Breathing and Swallowing

A disorder of swallowing (dysphagia) is a common sequela of neurodegenerative disorders (Buckholz & Robbins, 1997) and CNS damage such as stroke (Gordon, Hewer, & Wade, 1987; Martino et al., 2005). Up to 74.6% of stroke patients have swallowing disorders (Daniels et al., 1998) and between 15.2 and 20% of stroke patients will die from aspiration pneumonia within the first 12 months post-stroke (Scmidt, Smirnov, & Ryabova, 1988). Aspiration is a common sequela of dysphagia and can result in the development of aspiration pneumonia, a significant contributor to morbidity and mortality (Carter & Jancar, 1983). Closure of the glottis is deemed the primary mechanism in the prevention of aspiration (Medda et al., 2003; Shaker et al., 2003).

Dysphagia may be the result of incoordination between swallowing, mastication, and respiration (Logemann, 1988; Selley, Flack, Ellis, & Brooks, 1989b). The intimate association of neural controls of breathing and swallowing is highlighted by the recent report that acute stroke patients who present with dysphagia are more likely to demonstrate obstructive apnoeas than those stroke patients without dysphagia (Martinez-Garcia, Galiano-Blancart, Soler-Cataluna, Cabero-Salt, & Roman-Sanchez, 2006). This association is further emphasized by the simultaneous improvement of both apnoea and pharyngeal motor and sensory function (Martinez-Garcia et al., 2006). The importance of adequate coordination of breathing and swallowing is emphasized by the following statements: “aspiration results from oropharyngeal impairments with inadequate respiratory integration” (Morton, Minford, Ellis, & Pinnington, 2002, p. 192) and “aspiration, especially in elderly dysphagic patients, may be a consequence of primarily disturbed respiration” (Nilsson, Ekberg, Bulow, & Hindfelt, 1997, p. 503). This is supported by evidence of an increased incidence of post-swallow inspiration in neurological disorders in which aspiration is common, such as cerebral palsy (Rempel & Moussavi, 2005), stroke (Selley et al., 1989b), motor neurone disease, spinal cord and peripheral nervous system disease or damage (Hadjikoutis, Pickersgill, Dawson, & Wiles, 2000). Patients with respiratory disorders such as chronic obstructive airway disease also have a higher incidence of post-swallow inspiration (Shaker et al., 1992). There is a link between respiratory disorders such as hypercapnia and laryngeal penetration of swallowed materials (Nishino, Hasegawa, Ide, & Isono, 1998) which may therefore be the result of aberrant BSC.

Moreover, patients with Parkinson's disease (Pinnington, Muhiddin, Ellis, & Playford, 2000) and stroke (Leslie, Drinnan, Ford, & Wilson, 2002) are less likely to exhale after a swallow than healthy controls.

Post-swallow inspiration is more closely associated with patients with corticobulbar involvement than neurologically impaired patients who do not have damage to this area (Hadjikoutis et al., 2000). This suggests that suprabulbar structures may contribute to BSC (Hadjikoutis et al., 2000). Children with cerebral palsy exhibit a high incidence of post-swallow inspiration which "is significant; if the pharynx has not been cleared of bolus residue before the inspiration, the action may lead to aspiration" (McPherson et al., 1992, p. 585). Specifically, 24.5% of 5 ml liquid swallows in normal children are followed by inspiration compared to 39.5% and 54.6% in children with spasticity and athetosis, respectively. Swallowing at the expiratory-inspiratory cusp may be the most likely phase in which aspiration may occur since the latency of the onset of inspiration following a swallow at this cusp relative to the position of the bolus in the pharynx is shorter than swallows in the other respiratory-phase categories (Paydarfar, Gilbert, Poppel, & Nassab, 1995). The ingested bolus is positioned closer to the laryngeal vestibule at the onset of SA at this cusp (Paydarfar et al., 1995).

The importance of BSC in healthy human infant airway protection is unclear since "it appears that at less than 48 h postnatal age there is essentially no coordination between the swallow and breathing rhythms" (Bamford, Taciak, & Gewolb, 1992, p. 623). Infant anatomy may be more important than BSC in infant airway protection since the relatively high position of the larynx in infants and mammals is optimal for airway protection is deemed protective (Laitman & Reidenberg, 1993; Negus, 1943). This is supported by evidence that healthy preterm piglets do not aspirate despite premature spillage to the level of the pyriform recesses during inspiration and prior to the onset of swallowing (German, Crompton, & Thexton, 1998). This suggests that post-swallow inspiration is not essential to airway protection in mammals (German et al., 1998). Swallowing is deemed to be the primary protective mechanism in piglets (Page, Jeffery, Marks, Post, & Wood, 1995) and the same may apply to human infants given their comparable anatomy (Laitman & Reidenberg, 1993; Negus, 1943).

Although BSC appears to be a mechanism of lesser importance for airway protection in infants than in adults, prior research has suggested that there may be an ideal feeding pattern for human infants consisting of extended periods of coordinated breathing and swallowing

(Bamford et al., 1992). This is supported by clinical observation that assistance in taking regular breaths during feeding by withdrawing the food source from the infant may prevent apnoea-bradycardia and the development of deviant airway protection behaviours in the patient population (Matthews, 1994). The link between adequate cardiorespiratory control and efficient feeding (Daniels, Casaer, Devlieger, & Eggermont, 1986; Daniels et al., 1988; Daniels, Devlieger, Minami, Eggermont, & Casaer, 1990; Pinnington, Smith, Ellis, & Morton, 2000) also highlights the importance of well-coordinated breathing and swallowing. For example, post-swallow apnoea and inspiration occur more frequently in infants suffering from acute bronchiolitis (which results in tachypnea) than healthy infants (Pinnington, Smith et al., 2000). The feeding efficiency of the former group was less than the healthy controls; they consumed less milk despite an increase in swallowing frequency.

In term neonates the impact of feeding on respiration is marked and may be characterized by one or more of the following: reduced ventilation, tidal volume, and respiratory rate (Al-Sayed, Schrank, & Thach, 1994; Bamford et al., 1992; Mathew, Clark, Pronske, Luna-Solarzano, & Peterson, 1985). The immature nervous system of a newborn may be responsible for the incoordination of breathing and swallowing and may result in respiratory compromise (Reix et al., 2003). In both breast- and bottle-fed healthy term infants, oxygen saturation levels are lower following a feed than during feeding (Hammerman & Kaplan, 1995). Thus, it is not surprising that respiratory disease may limit an infant's ability to feed effectively (Stevenson & Allaire, 1991). This was demonstrated in preterm infants. The rate of both sucking and swallowing decreased with an increase in respiratory drive induced by carbon dioxide inhalation during nutritive feeding (Timms, DiFiore, Martin, & Miller, 1993). According to Hall (2001) respiratory compromise may indirectly lead to poor feeding 'endurance' in infants. This may be the result of increased workload during breathing which, paired with a weak suck, may result in an uncoordinated suck-swallow-breathe sequence and subsequent fatigue. Given the importance of the coordination of breathing and swallowing, determining the neural mechanisms that control this function is imperative if pathology is to be understood and treated appropriately.

2.2 The Neuroanatomy of Breathing-Swallowing Coordination

2.2.1 The Neuroanatomy of Respiration

The glossopharyngeal and vagus nerves supply the chemoreceptors in the carotid arteries that detect the level of blood oxygenation (Kiernan, 1998). This sensory information is carried to the nucleus tractus solitarius (NTS) in the medulla (Figure 2.1) by these two nerves (Kiernan, 1998). Further neural processing by the inspiratory, expiratory and pneumotaxic centres in the brainstem (explained in greater detail below) result in altered respiratory rate or depth (Kiernan, 1998) which occurs via the vagus, phrenic, and thoracic efferent nerves that supply the intercostals muscles and diaphragm (Rontal & Rontal, 1976).

The medulla and the pons in the brainstem (Figure 2.2) house the central pattern generators for respiration and are crucial for the generation and preservation of breathing (Horn & Waldrop, 1998). A central pattern generator (CPG) is a small neural network within the CNS that has an "operational expression to designate an ensemble of neural elements whose properties and connectivity can give rise to characteristic patterns of rhythmic activity in the absence of external feedback" (Rossignol & Dubuc, 1994, p. 895).

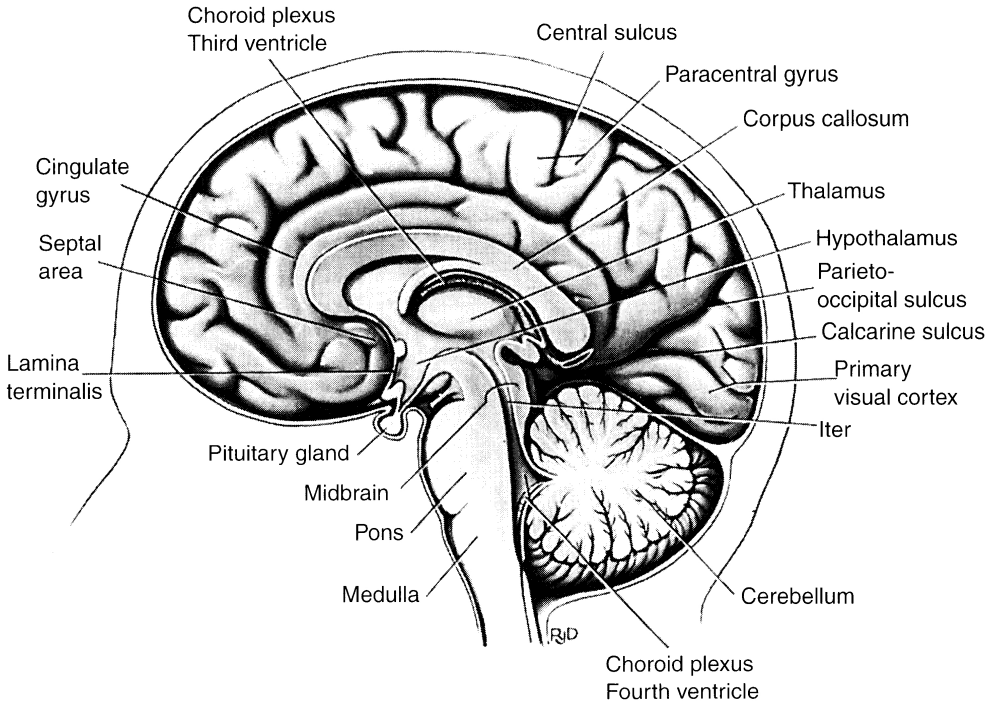


Figure 2.1 Sagittal view of the gross anatomy of the human brain. From Steward, O. (2000). Functional Neuroscience. New York: Springer-Verlag.

There are at least two brainstem CPGs that control respiratory rhythm (review by Sawczuk & Mosier, 2001). The first is the pneumotaxic centre (including the nucleus parabrachialis medialis and the Kolliker-Fuse nucleus) in the pons, which may control the switching between inspiration and expiration (Sawczuk & Mosier, 2001). The second includes the

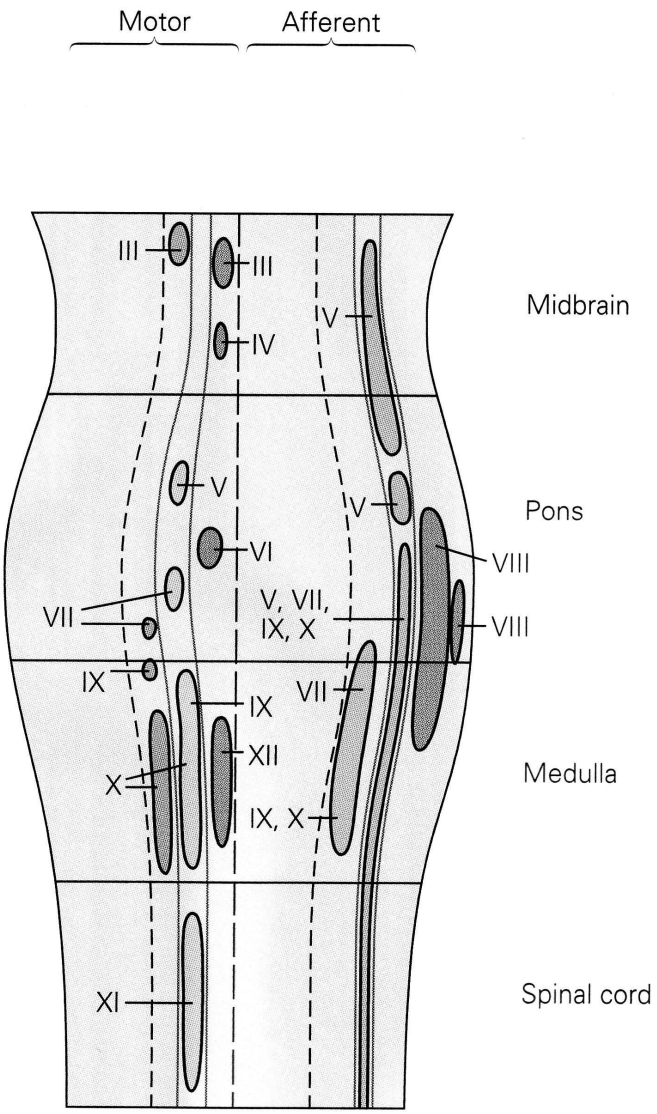


Figure 2.2 A schematic view of the brainstem (pons, medulla, and midbrain) and spinal cord housing the motor and sensory (afferent) nuclei of the cranial nerves: I = olfactory, II = optic, III = oculomotor, IV = trochlear, V = trigeminal, VI = abducens, VII = facial, VIII = vestibular, IX = glossopharyngeal, X = vagus, XI = spinal accessory, and XII = hypoglossal. The nucleus tractus solitarius consists of the nuclei of cranial nerves VII, IX, and X. The nucleus ambiguus consists of the nuclei of cranial nerves IX and X. Adapted from Kandel, E. R., Schwartz, J. H., & Jessell, T. M. (2000). Principles of Neural Science (4th ed.). New York: McGraw-Hill.

respiratory groups (dorsal and ventral) in the medulla (Sawczuk & Mosier, 2001), which house the pre-Botzinger complex considered to be the respiratory ‘pacemaker’ (Smith et al., 1991). The neural firing patterns of the dorsal respiratory group (around the NTS) indicate that it is principally inspiratory-related whereas the ventral respiratory group (around the nucleus ambiguus, NA) contains both inspiratory- and expiratory-related neurones in animals (review by Cohen, 1981). Brainstem respiratory centres automatically control the muscles of respiration via the bulbospinal pathway (Straus, Locher, Zelter, Derenne, & Similowski, 2004).

Although brainstem control of respiration is vital, respiration can be consciously altered (Horn & Waldrop, 1998; Mador & Tobin, 1991) which implies that the respiratory CPG can be modified by the cortex (Davenport & Reep, 1995). Foetal breathing-like activities appear stimulated by heightened neural activity in the cortical and subcortical structures (Blanco, Hanson, & Kumar, 2000). Respiration is also affected by alterations in mental activity which suggests that higher brain centres influence respiratory pattern variability (Mador & Tobin, 1991).

There is considerable evidence from positron emission tomography (PET) studies supporting cortical control of respiration in animals and humans. Specifically, the following respiratory-related cortical areas have been identified: orbital cortex, fronto-orbital regions, motor precruciate region, a region caudal to the ansate sulcus, posterior sigmoid gyrus, anterior suprasylvian gyrus and sulcus, anterior ectosylvian gyrus, anterior sylvian gyrus, cruciate gyrus and sulcus, anterior sigmoid gyrus, marginal gyri, postrolandic sensory cortex, motor and sensory areas of the anterior and posterior sigmoid gyrisomatosensory and motor cortices, and the mesocortex (review by Davenport & Reep, 1995). Volitional breathing, specifically, excites the premotor cortex (Colebatch et al., 1991; Fink et al., 1996), the primary motor cortex (Colebatch et al., 1991; Evans et al., 1999; Fink et al., 1996), the supplementary motor cortex (Figure 2.3) (Colebatch et al., 1991; Evans et al., 1999), and the inferolateral sensorimotor and parietal cortices (Fink et al., 1996).

Further evidence of cortical respiratory control is offered by stimulation studies cited in a review by Davenport and Reep (1995). Stimulation of the vagus, superior laryngeal, intercostals, and phrenic nerves activate areas within the cortex (Davenport & Reep, 1995). For example, vagus nerve stimulation results in excitatory or inhibitory responses in thalamic nuclei, such as the anterior medial and paracentral nuclei, some of which have connections to

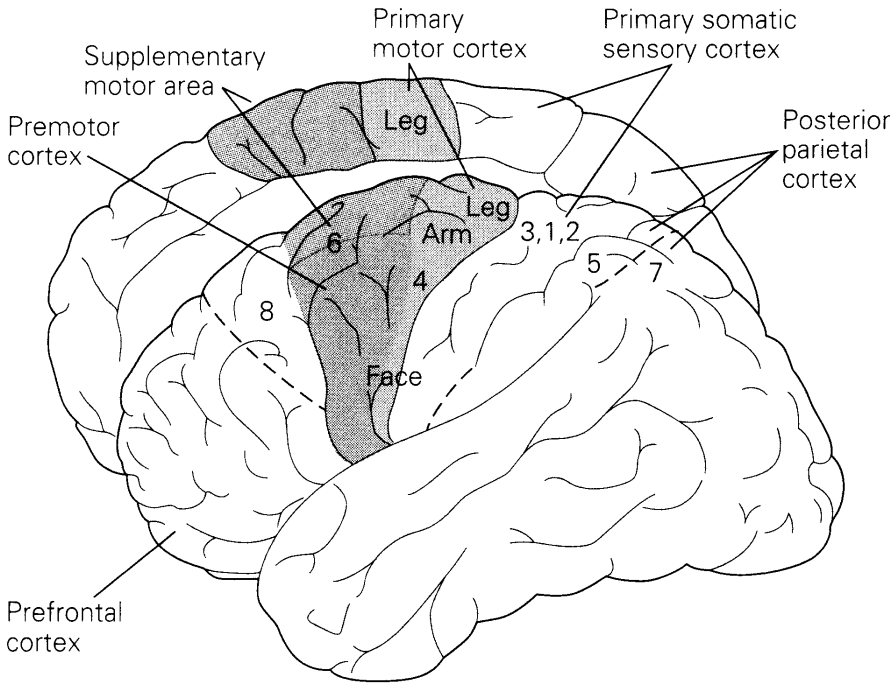


Figure 2.3 Key sensori-motor areas of the human cortex. From Kandel, E. R., Schwartz, J. H., & Jessell, T. M. (2000). Principles of Neural Science (4th ed.). New York: McGraw-Hill. Numbers 1 - 8 indicate Brodmann's areas: the primary somatosensory cortex is represented by areas 1, 2, and 3, the primary motor cortex is represented by area 4, the somatosensory association cortex is represented by areas 5 and 7, and the frontal visual area is represented by area 8 (Fix, 1995).

the mesocortex and motor cortex (Hallowitz & MacLean, 1977). Cortical stimulation alters respiratory rate in animals (Kaada, 1951; Spencer, 1894) and influences phrenic nerve inspiratory activity suggesting that inspiration may in part be cortically mediated (Thompson, Davenport, & Warner, 1987). Transcranial magnetic stimulation studies of the human motor cortex influences diaphragmatic activity (Lefaucheur & Lofaso, 2002; Murphy et al., 1990).

The functional importance of the aforementioned respiratory-related cortical sites is highlighted by clinical evidence of patients with pontine (e.g., 'locked in' syndrome) and medullary (e.g., Ondine's curse) damage which supports the contribution of supramedullary input in volitional respiratory control (Moss, 2005). Patients with Ondine's curse are forced to consciously breathe in order maintain respiratory activity to survive and patients with 'locked-in' syndrome have lost the ability to volitionally alter respiration although autonomic respiratory function is preserved (Moss, 2005). In summary, although "the pontomedullary oscillator is essential for basal respiratory homeostasis, the brain as a whole is required for normal breathing, and that the wakefulness stimulus and intact corticospinal pathways are

crucial for maintaining stable, versatile, and appropriately adaptive breathing patterns" (Moss, 2005, p. 295).

Supramedullary influences are particularly evident during the volitional control of respiration (review by Moss, 2005) which is thought to engage corticospinal pathways (Straus et al., 2004). An example of corticospinal connection is the projection from the cortex to respiratory-related motor neurones, such as the phrenic and thoracic nerves (Rikard-Bell, Bystrzycka, & Nail, 1985). However, there are other respiratory-related pathways between the cortex and subcortical sites. This is demonstrated by animal research. The rat prefrontal cortex and midbrain periaqueductal gray are connected to one another (Beitz, 1982) and the motor cortex is connected to the hypothalamus in cats (Baev, Berezovskii, Kebkalo, & Savos'kina, 1985).

The respiratory-related subcortical structures that have been identified include the basal ganglia (Fink et al., 1996), various regions in the midbrain (Cameron, 1995; Martin & Booker, 1878; Orem, 1982) such as the hypothalamus (Fink et al., 1996; Vertes & Crane, 1996), and the cerebellum (Gozal et al., 1994). The respiratory-related afferent cortico-subcortical pathways may consist of two relatively independent cortical respiratory pathways, one for respiratory muscle afferents and another for vagus and possibly phrenic nerves (Davenport & Reep, 1995). Both systems pass through the brainstem but the first one projects to the oralis portion of the thalamic ventroposterior nucleus via the medial lemniscal tract, which in turn project to the sensorimotor cortex. The connection to the sensorimotor cortex is thought to serve an integrative function for cortically initiated movements. The second system projects from the brainstem to the amygdala, which in turn projects to the mesocortex and the medial dorsal nucleus. The involvement of the amygdala and hypothalamus suggests that this pathway is involved in the affective alteration of respiration (Davenport & Reep, 1995).

Although the descending tracts for these two cortical respiratory pathways differ, the motor cortex and mesocortex of the respective pathways are connected (Davenport & Reep, 1995). This suggests an interaction between the two relatively independent pathways (Davenport & Reep, 1995). The first descends from the motor area in the cortex to the spinal respiratory muscle motorneurones possibly synapsing in the brainstem. The second descends from the mesocortex to the brainstem via the amygdala and hypothalamus (Davenport & Reep, 1995).

The role of afferent connections between the vagus nerve and the somatosensory and motor cortex in the cortical control of respiration is unclear (Davenport & Reep, 1995) and, despite the abundance of literature supporting cortical respiratory influence, the precise mechanisms of cortical input are not well established (Horn & Waldrop, 1998). Suprabulbar involvement may be primarily during 'ventilatory challenges' such as alteration of respiration under conditions such as exercise, hypoxia, hypercapnia, and thermal changes (Horn & Waldrop, 1998). The impact of feeding on infant cardio-respiratory function (Bamford et al., 1992) suggests that feeding is a 'ventilatory challenge', and may thus demand suprabulbar respiratory control.

In summary, the brainstem houses the CPGs for respiratory phase cycling but suprabulbar respiratory-related structures have also been identified. As will be shown, the same applies to the neural controls of swallowing; predominantly brainstem-generated pattern of muscles activation are under some influence of suprabulbar structures. The CPGs for breathing and swallowing in the brainstem are functionally distinct (Sawczuk & Mosier, 2001) but the respiratory-related neural sites and their respective connections are not too dissimilar to those involved in swallowing.

2.2.2 The Neuroanatomy of Swallowing

Oropharyngeal swallowing is a complex process involving a total of 32 pairs of muscles including those of the lips, tongue, jaw, soft palate, larynx, pharynx, and upper oesophageal sphincter (UOS) (Guyton, 1986), five cranial nerves, and two cervical nerves, discussed below (Perlman & Christensen, 1997). The sequence of swallowing events may be classified into three stages (Figure 2.4): oral, pharyngeal, and oesophageal (Morrell, 1984). A summary of the afferent and efferent innervation of swallowing can be found in Appendix A, however the focus of further discussion will be on the pharyngeal stage.

The pharyngeal stage of swallowing is primarily reflexive (Morrell, 1984) and in adults, it takes approximately 800 ms to complete (McConnel, Cerenko, Jackson, & Guffin, 1988). During the 800 ms, the following primary events occur: the bolus is propelled into the pharynx by the tongue, the epiglottis deflects vertically, the glottis closes (true vocal fold adduction), the larynx elevates, the UOS opens, and the pharyngeal muscles and tongue propel the bolus through the UOS into the oesophagus (Figure 2.5) (Morrell, 1984). The cranial nerves responsible for the afferent innervation of the pharyngeal stage include the

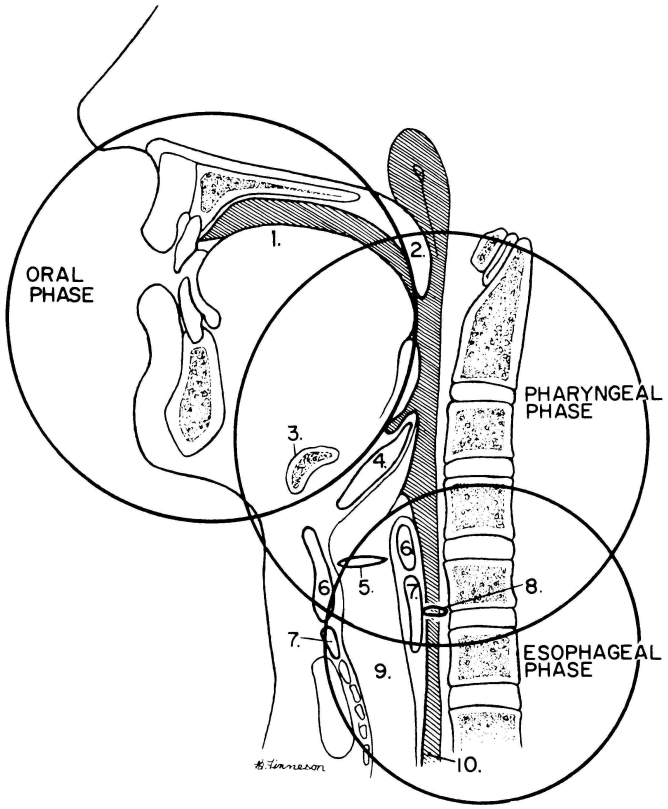


Figure 2.4 The key structures of the head and neck involved in the three stages of swallowing: tongue (1), soft palate (2), hyoid bone (3), epiglottis (4), true vocal folds (5), thyroid cartilage (6), cricoid cartilage (7), upper oesophageal sphincter (8), trachea (9), and oesophagus (10) . From Bass, N. H., & Morrell, R. M. (1992). The neurology of swallowing. In M. E. Groher (Ed.), Dysphagia Diagnosis and Management (2nd ed., pp. 1-29). Stoneham, MA: Butterworth-Heinemann.

trigeminal, facial, glossopharyngeal, and vagus nerves (Perlman & Christensen, 1997). These four nerves, the hypoglossal nerve, and cervical nerves (C1 and C2) provide efferent innervation (Perlman & Christensen, 1997).

Those nerves, structures, and muscles involved in airway closure and protection against aspiration during the pharyngeal stage are of particular relevance (i.e., sensation to the laryngopharynx and epiglottis, hyolaryngeal excursion, laryngeal closure, and epiglottic deflection). Afferent innervation of the laryngopharynx and epiglottis includes the internal branch of the SLN of the vagus nerve (Perlman & Christensen, 1997). The recurrent laryngeal branch of the vagus provides afferent innervation below the level of the vocal folds (Perlman & Christensen, 1997). The recurrent branch of the vagus nerve also supplies efferent innervation to the muscles that are responsible for laryngeal closure and the vertical collapse

of the glottis during swallowing (Perlman & Christensen, 1997). The submental/floor of mouth muscles that are responsible for the hyolaryngeal excursion, laryngeal elevation, and subsequent epiglottic deflection are the mylohyoid (trigeminal), geniohyoid (hypoglossal and C1 and C2), stylohyoid (facial), and anterior digastric muscles (trigeminal) (Morrell, 1984; Perlman & Christensen, 1997).

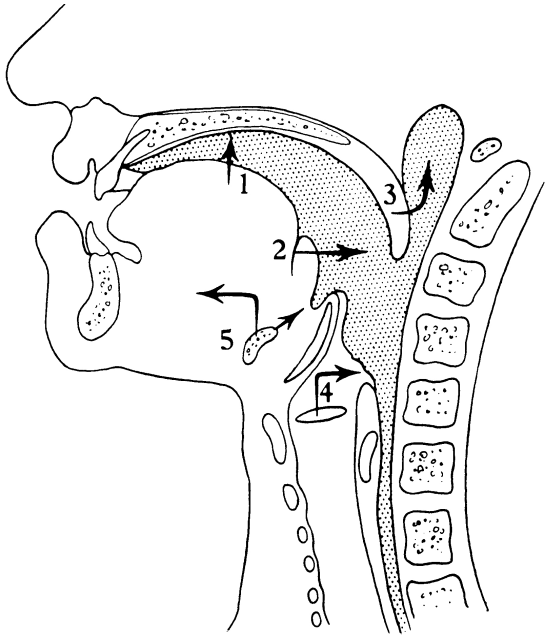


Figure 2.5 Summary of the five key physiological features of a swallow: (1) tongue movements, (2) base of tongue makes contact with the soft palate and posterior pharyngeal wall, (3) soft palate elevates, (4) larynx elevates and the pharynx narrows, and (5) the epiglottis deflects downwards as the hyoid bone moves up and forwards. From Donner, M. W., & Siegel, C. (1965). The evaluation of neuromuscular disorders by cineradiography. American Journal of Roentgenology, 94, 299-307.

Afferent swallowing information converges in the NTS (Figure 2.6) where it is processed and the motor pattern for the execution of the swallow is designed. Brainstem control is fundamental to swallowing (Jean, 1984; Miller, 1972, 1982; Sessle & Henry, 1989) with the neurones and interneurones important to swallowing are primarily found in the pons and medulla, and to a lesser extent in the midbrain (Miller, 1999). The site responsible for the initiation of swallowing is the NTS (Mrini & Jean, 1995) and the sites responsible for the modification of swallowing are the NA and reticular formation (review by Sawczuk & Mosier, 2001).

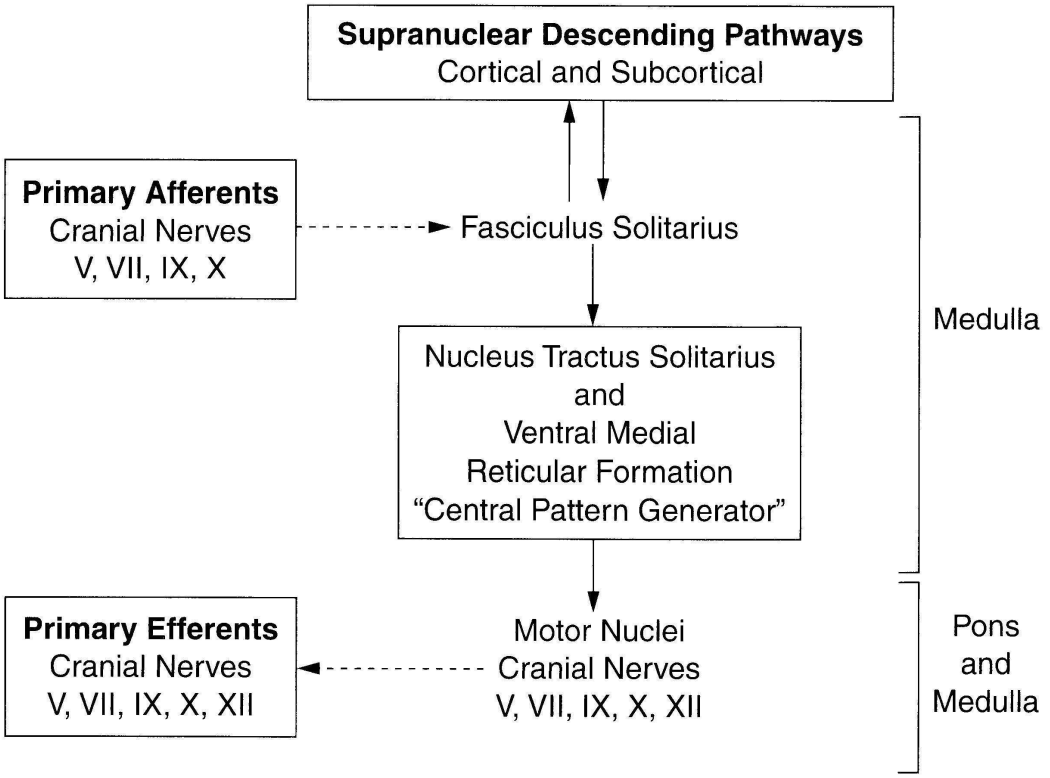


Figure 2.6 A schematic summary of the peripheral and central neural controls of swallowing. From Arvedson, J. C., & Brodsky, L. (2002). Pediatric Swallowing and Feeding: Assessment and Management (2nd ed.). New York: Singular Publishing Group.

Electrical stimulation of two specific sites close to the trigeminal motor nucleus in the pons evoke swallowing: the reticular formation, and the region anterior to the trigeminal nucleus (Miller, Bieger, & Conklin, 1997). Many studies cited by Martin and Sessle (1993) in their review have shown that electrical stimulation of cortical sites such as the anterolateral frontal and pericentral cortices also elicit swallowing in animals (sheep, cattle, monkeys, and rabbits) and humans (Car, 1970; Miller & Bowman, 1977; Sumi, 1969), but swallowing-related cortical and subcortical regions are not essential to the coordination of the swallow (Miller et al., 1997). Infants with severe neural damage located superior to the midbrain and adults with severe cortical damage can still swallow (Miller et al., 1997). Even before the maturation of cortico-subcortical pathways, normal human foetuses exhibit coordinated swallowing behaviour (Doty, 1968). Similarly, intra-oral stimulation of decerebrate animals can elicit licking, chewing, and pharyngeal swallowing (Doty & Bosma, 1956; Doty, Richmond, & Storey, 1967; Grill & Norgren, 1978; Miller & Sherrington, 1916; Thexton & Griffiths, 1979). Furthermore, anencephalic human infants can suck and swallow (Monnier & Willi, 1953). Thus, the importance of brainstem control of swallowing over that of the cortex is well-established.

Early cortical input into swallowing of neonates may be minimal since infant feeding is considered to be reflexive (Stevenson & Allaire, 1991). However, cortical activity specific to feeding has been reported in healthy human neonates (Lehtonen et al., 1998). Furthermore, during postnatal development in the guinea pig, cortical shifts coincide with changes in feeding-related oral movements (Iriki, Nozaki, & Nakamura, 1988). A 'cortical sucking area' in neonatal guinea pigs was located by electrical stimulation. This area disappeared and a 'cortical masticatory area' appeared during transition from sucking to chewing during postnatal development. Both the cortical sucking and masticatory areas receive projections from the reticular nucleus, thereby indicating a maturational shift in cortical projection from these areas during feeding maturation. The emergence of mastication is likely the result of CNS maturation and the development of dentition (Miller, 1999). However, guinea pigs are born with all their permanent teeth, thus the transition from sucking to chewing cannot be the result of eruption of teeth but rather that the cortex and the pyramidal tract undergo major postnatal reorganisation (Iriki et al., 1988).

In adults there is considerable evidence for the role of the cortex in swallowing. Lesion and intracortical microstimulation studies identified the following swallowing-related cortical sites: the human insular cortex (Daniels & Foundas, 1997; Daniels, Foundas, Iglesia, & Sullivan, 1996; Stickler, Gilmore, Rosenbek, & Donovan, 2003) and many cortical regions in the primate such as the tongue primary motor cortex, facial regions of the primary motor and somatosensory cortices, and the cortical masticatory region (Martin et al., 1999; Martin, Murray, Kemppainen, Masuda, & Sessle, 1997). An EEG study of premotor potentials indicated that voluntary swallowing activates the supplementary motor cortex but not necessarily the primary motor cortex (Huckabee et al., 2003). This is supported by EEG research indicating that the primary sensorimotor and SMAs are involved in volitional swallowing in humans (Satow et al., 2004). Functional magnetic resonance imaging (fMRI) identified the following cortical sites as active during swallowing: primary sensory and motor areas, SMA, premotor cortex, posterior parietal cortex, cingulate gyrus, inferior frontal gyrus, cerebellum, insular cortex, auditory cortex, corpus callosum, basal ganglia, and thalamus (Mosier & Bereznaya, 2001). This neuroimaging study identifies multiple cortical sites that are active during swallowing, but their specific roles are unknown. It has been suggested that areas such as the anterior cingulate, motor/premotor cortex, insula, and occipital/parietal region that are activated during volitional swallowing tasks (as per fMRI) are actually

representative of swallowing-related activities such as “jaw clenching, lip pursing, and tongue rolling” (Kern, Birn et al., 2001, p. 531).

The cortex is thought to play a major role in the voluntary initiation of swallowing but not in spontaneous (reflexive/naïve/automatic) swallowing (review by Ertekin & Aydogdu, 2003). However, some reflexive components of swallowing may be subject to the influence of descending cortical excitation and inhibition (Ertekin & Aydogdu, 2003). This is evident from suprabulbar lesions resulting in impaired UOS (Ertekin, Aydogdu, Tarlaci, Turman, & Kiylioglu, 2000). Similarly, fMRI studies have shown cortical activation during reflexive swallowing, albeit less than for volitional (purposeful/on-command) swallows (Kern, Jaradeh et al., 2001; Martin, Goodyear, Gati, & Menon, 2001). Reflexive and volitional swallowing resulted in the activation of many similar cortical sites (i.e., primary sensory/motor cortex) but only volitional swallowing activated the insular cortex, prefrontal/cingulate gyrus, cuneus, and precuneus region. Kern et al. (2001) summarize “the activation of non-sensory/motor cortical regions observed in volitional swallowing probably represent the volitional aspects of the swallow such as intent, urge, decision-making, and memory, as well as information processing related to deglutition” (p. 358). However, there is some doubt as to whether these were truly reflexive swallows as they were elicited by the introduction of a liquid bolus into the pharynx at regular intervals (every 30 s) and, thus, anticipation of the bolus cannot be ruled out. Nonetheless, more recent research has found no difference in the magnitude of cortical activation between: dry swallows on command, spontaneous dry swallows, and irrepressible swallows (Kern, Hofmann, Jesmanowicz, & Shaker, 2003).

Reflexive and volitional swallowing activate similar areas in the cortex but the caudal anterior cingulate cortex is more likely associated with voluntary swallowing conditions than non-volitional (Martin et al., 2001). These authors defined ‘reflexive’ swallows as those performed by participants after they “were instructed to relax and remain still without altering their vegetative functions such as breathing and swallowing” (Martin et al., 2001, p. 939). This instruction possibly drew the participants’ attention to such behaviours and thereby added a volitional component to the task. Similarly, other studies have attempted to capture ‘subconscious’ swallows while participants rested (but did not sleep) in a quiet room, without an obvious attempt to distract these participants from their swallowing performance (Nishino, Yonezawa, & Honda, 1985; Shaker et al., 1992).

Determining the exact nature of the swallowing-related cortical sites is difficult for two reasons. Much of the research into the role of the cortex in swallowing has been on nonhuman subjects (e.g., Iriki et al., 1988; Narita, Yamamura, Yao, Martin, & Sessle, 1999; Yamamura et al., 2002), thus the applicability to human cortices, which are more developed than those of animals, may be limited. Moreover, the various methods used to identify the neural networks of swallowing, such as lesion analysis, electrical and transcranial magnetic stimulation, and functional brain imaging techniques (PET and fMRI) are inherently limited in the information they can provide regarding the nature of the input of the cortical sites in swallowing. These are discussed below and advocate a behavioural approach in the study of swallowing respiratory coordination.

Temporal sensitivity of neuroimaging techniques is particularly relevant to the measurement of behaviours such as swallowing since the behaviour involves a sequence of temporal activation of the respective parts of the brain. Neuroimaging of swallowing behaviour identifies some of the specific parts of the brain that are activated but correlation with specific physiological events is difficult. An adult pharyngeal swallow takes approximately 800 ms to complete (McConnel et al., 1988), and involves the sequential activation of 32 pairs of muscles (Guyton, 1986), thus making it difficult to pair cortical excitation with specific physiological and biomechanical components of the swallow. Similarly for the study of BSC, there is a tight temporal synchronisation of the components of respiration and swallowing. For example, the onset of the pharyngeal stage of swallowing typically occurs after the onset of SA by a mean of 442 ± 1285 ms (Martin-Harris et al., 2003). Such temporal resolution is beyond what is offered by current neural imaging techniques (e.g., approximately 40 s for PET and 4 s for fMRI) (Aine, 1995), thus identifying the CNS sites that influence the relative onsets and offsets of the constituents of respiration and swallowing is difficult at best.

In terms of spatial resolution, both PET (Maquet, 2000) and fMRI (Aine, 1995) are problematic. PET quantifies regional cerebral blood flow and glucose metabolism which indicate neural activity (Krasuski, Horwitz, & Rumsey, 1996). However, as a result of restricted spatial resolution, PET takes the average level of activity from many neurones, of which only a small portion may actually be active (Maquet, 2000). The spatial resolution of FMRI, on the other hand, is limited in part by vascular changes in the brain associated with respiration (Aine, 1995).

Spatial insensitivity is also a major limitation of transcranial magnetic stimulation which has been used to map the cortical representation of swallowing musculature in many studies (Fraser et al., 2002; Hamdy, Aziz, Hobson, & Thompson, 1996; Hamdy, Aziz, Rothwell, Hobson, & Thompson, 1998; Hamdy, Aziz, Rothwell, Power et al., 1998; Hamdy, Xue, Valdez, & Diamant, 2001; Valdez, Salapatek, Niznik, Linden, & Diamant, 1993). Cortical stimulation is provided by a hand-held coil positioned above the surface of the scalp, thus positional inaccuracies can easily result in spatial inaccuracies. Furthermore, transcranial magnetic stimulation studies evaluate pharyngeal muscle activity in response to cortical stimulation and do not evaluate the functional role of these muscles in swallowing. In order to prevent the induction of epileptic seizures in humans, the magnetic pulses employed by the transcranial magnetic stimulation technique are given slowly (Hamdy, Xue, Valdez, & Diamant, 1999) and at a low intensity (Hamdy et al., 2001). At the low intensities used in transcranial magnetic stimulation studies on humans, actual swallowing behaviour is not elicited (Hamdy, Xue et al., 1999). This is potentially problematic when inferring the results to functional swallowing. Furthermore, swallowing is the end result of the synchronization of multiple neuromuscular events modulated, in part, by afferent feedback (Miller, 1999).

Given the methodological difficulties with current neuroimaging and stimulation techniques, the exact nature of swallowing-related cortical sites is unknown. Even the central control of isolated components of swallowing, like tongue movement, is not clear (review by Sawczuk & Mosier, 2001). The role of the cortex in swallowing ranges from voluntary initiation, preparation, and mastication. The primate lateral pericentral cortex is thought to be involved in the initiation of swallowing since bilateral deactivation of this area results in difficulties initiating swallowing (Narita et al., 1999). This is supported by the findings that hemispheric stroke in humans may result in an inability to initiate a dry swallow (Weber et al., 1991). Cold-block deactivation of the primate motor cortex affects the oral manipulation/preparatory phase of swallowing thereby highlighting its role in mastication and swallowing preparation (Yamamura et al., 2002).

Mosier and Bereznaya (2001) speculated that the cortex is involved in swallowing sensory integration. These speculations were drawn from analogies made between swallowing and other sensorimotor functions of the cortical sites activated by swallowing. For example, the secondary sensory cortex, inferior frontal gyrus, basal ganglia-thalamocortical loops, and cerebellum considered to be involved in sensorimotor integration of non-swallowing-related activities, may therefore be involved in sensorimotor integration during swallowing (Mosier

& Bereznaya, 2001). The insular cortex may be involved in the synchronisation of the kinematics of swallowing and the cerebellum may be involved in the adaptive modulation of the swallowing response (in particular the tongue and pharyngeal muscles) based on sensory input (Mosier & Bereznaya, 2001). However, these analogies remain unsubstantiated and, according to Ertekin and Aydogdu (2003), the interaction of the multiple swallowing-related cortical sites requires much more research before functional activation patterns are properly understood.

In conclusion, the literature supports a cortical role in the initiation, modification, sensorimotor integration, and temporal adaptation of swallowing as a function of degree of volitional input.

2.2.3 The Neuroanatomy of the Coordination of Breathing and Swallowing

Given that breathing does not continue during the completion of a pharyngeal swallow in human infants and adults (Hiss, Strauss, Treole, Stuart, & Boutilier, 2003; Martin-Harris, Michel, & Castell, 2005; Stevenson & Allaire, 1991; Sumi, 1967; Thach & Menon, 1985; Weber, Woolridge, & Baum, 1986; Wilson et al., 1981), it is likely that these two functions are controlled by distinct neural networks. Neural networks, which may share neurones, may dedicate themselves to one or the other function (Shiba, Satoh, Kobayashi, & Hayashi, 1999), therefore such functions cannot be performed simultaneously. The possible sites that control this switch between these two functions and govern the pattern of BSC are discussed below.

The primary CNS site responsible for coordinating breathing and swallowing appears to be the brainstem. Many authors have acknowledged or demonstrated significant brainstem contribution to BSC in humans and animals (Dick, Oku, Romaniuk, & Cherniack, 1993; Feroah, Forster, Fuentes, Lang et al., 2002; Lewis, Bachoo, Polosa, & Glass, 1990; McFarland & Lund, 1993; Miller & Sherrington, 1916; Nishino & Hiraga, 1991; Nishino et al., 1985; Saito et al., 2002; Smith, Wolkove, Colacone, & Kreisman, 1989; Wilson et al., 1981). Few, though, have suggested the possibility that suprabulbar structures (Kelly et al., in press) or the corticobulbar tract (Hadjikoutis et al., 2000) may be involved in modifying BSC.

The effect of swallowing on respiration demonstrates the close relationship of these two phenomena. It is generally accepted that swallowing interrupts respiratory rhythms (Clark, 1920; Doty & Bosma, 1956; McFarland & Lund, 1993, 1995; Miller & Sherrington, 1916;

Nishino et al., 1985; Preiksaitis et al., 1992; Smith et al., 1989). Bursts of non-nutritive swallows in term healthy infants result in a slowing of breathing rate (Bamford et al., 1992) yet in elderly adults, the respiratory rate increases immediately after swallowing (Hirst, Ford, Gibson, & Wilson, 2002). The age-related influence of swallowing on breathing may be a function of an interaction of age and phase of respiration in which the swallow occurs (Nishino & Hiraga, 1991; Nishino et al., 1985; Smith et al., 1989; Wilson et al., 1981). For example, a slowing of respiratory rate was observed only for swallows occurring in the inspiratory phase in young adults (Nishino et al., 1985). The phase-specific effects may explain the conflicting evidence that swallowing may either lengthen (McFarland & Lund, 1995; Nishino et al., 1985; Palmer & Hiiemae, 2003) or shorten (Nishino & Hiraga, 1991; Smith et al., 1989; Wilson et al., 1981) the duration of the respiratory cycle in which it occurs. In young adults, a lengthening effect may be only observed for the respiratory cycle that follows the swallow (Preiksaitis et al., 1992).

A similar effect is observed in animals. Swallowing may result in an increase in the duration of the respiratory phase in which swallowing occurs, as well as subsequent respiratory cycles (Miller & Sherrington, 1916). In order to examine the effects of swallowing on respiration in animals, most studies induced swallowing by superior laryngeal nerve (SLN) stimulation (Dick et al., 1993; Lewis et al., 1990; Miller & Sherrington, 1916; Saito et al., 2002). SLN stimulation is a commonly used and effective method of eliciting swallowing (Doty, 1951, 1968; Miller, 1982; Miller & Loizzi, 1974; Saito et al., 2002; Saito et al., 2003; Sumi, 1970). Stimulation of this nerve may result in complete cessation of respiration in unanaesthetized animals (Donnelly & Haddad, 1986), even in the absence of a pharyngeal swallow (Miller & Loizzi, 1974). SLN stimulation may also result in a disruption in respiratory timing in decerebrate, unanaesthetized cats (Lewis et al., 1990), or a slowing of respiratory rate (Dick et al., 1993). Even when the stimulation is given at a very low intensity and swallowing is not elicited, the duration of the expiratory phase still increases (Dick et al., 1993).

The interaction between swallowing and respiratory control mechanisms is demonstrated by the observation that the neurones responsible for depressing expiration (‘decrementing-expiratory neurones’) in the brainstem of decerebrate rats are primarily activated during a swallow while those responsible for augmenting expiration are only activated after the swallow and prior to the activation of the inspiratory neurones (Saito et al., 2003, p. 338). These phenomena may account for the suppression of expiration during swallowing (swallowing apnoea) and the post-swallow expiratory pattern typically observed in humans

(Saito et al., 2003). Saito et al. (2003) acknowledged that, although the mechanisms controlling the order of excitation and inhibition are not clear, they are most likely brainstem-generated.

As in humans, the effect of swallowing on respiration is phase-specific in animals (Feroah, Forster, Fuentes, Lang et al., 2002). This is supported by the findings of three studies, which provide insight into the evaluation of swallowing-respiratory neural circuitry. First, electrical stimulation of the internal branch of the SLN nerve of anaesthetized cats during inspiration but not during expiration evoked phrenic nerve excitation (Berger & Mitchell, 1976). This suggests a phase-dependant effect of swallowing on the function of respiratory-related peripheral nerves. Second, SLN stimulation influenced the latency of the triggered fictive swallow of anaesthetized decerebrate rats depending on the phase of respiration in which stimulation occurred; mid-inspiratory SLN stimulation resulted in a delayed swallow (Saito et al., 2002). Furthermore, SLN stimulation activated inspiratory-related neurones (and expiratory–related neurones, but to a lesser degree) as well as swallowing-related neurones in the rat brainstem. Only three of the 56 respiratory-related neurones activated by swallowing-related behaviours were expiratory-related (Saito et al., 2002). Similarly, Saito et al. (2003) later showed that all brainstem ‘augmenting expiratory neurones’ were inactive during swallowing in rats. In contrast, earlier research found that only half of the inspiratory and the vast majority of expiratory neurones are active during swallowing in felines (Sumi, 1963). Nonetheless, Saito et al. (2002, p. 1058) concluded that it is likely the NTS is responsible for the “reciprocal inhibition between swallowing and inspiration” which may account for the high occurrence of post-swallow expiration typically observed in humans (Hiss et al., 2001).

The third study that supports a phase-dependant effect of swallowing on respiration highlights the communication between the CPGs for respiration and swallowing, specifically the relationship between expiration and swallowing (Dick et al., 1993). Fictive swallowing induced by SLN stimulation of decerebrate, vagotomized, paralysed and ventilated cats had a variable effect on respiratory phase duration of individuals (Dick et al., 1993). Fictive swallowing occurred either at the inspiratory-expiratory or expiratory-inspiratory cusps (Dick et al., 1993). Unfortunately, fictive swallowing was defined as short bursts of activity in the thyroarytenoid and hypoglossal nerves (Dick et al., 1993) which may not represent a coordinated swallow response. In addition, the thyroarytenoid and hypoglossal nerves are also involved with other activities such as voicing and licking respectively, thus the applicability of the findings of Dick et al. (1993) to a coordinated oro-pharyngeal swallow may be limited.

Further support for the interaction of CPGs is offered by the finding that swallowing, respiration, and mastication influence the behavioural patterns of one another (McFarland & Lund, 1995). This is echoed by the observation that vocalization and swallowing alter the firing patterns of respiratory-related neurones in the ventral medulla of monkeys (Larson et al., 1994). However, it is unclear whether the CPGs for breathing and swallowing are distinct entities with one influencing the other (McFarland & Lund, 1995; Paydarfar et al., 1995) or whether the CPGs share at least some neural substrates (Dick et al., 1993).

Support for distinct respiratory and swallowing neural pools is in the largely concurrent execution of SA and swallowing. Since both SA (Hiss et al., 2003; Nishino & Hiraga, 1991) and swallowing are centrally governed events, respiratory-inhibiting neurones cannot be simultaneously active in the execution of swallowing and are therefore distinct from swallowing-related neurones. However, this may be true for some but not all respiratory- and swallowing-related neurons. Some swallowing-related neurones are also involved in respiratory control implying at least a small overlap in breathing and swallowing neural substrates (review by Jean, 2001). Shared respiratory- and swallowing-related brainstem regions have been found in felines (Oku et al., 1994). Moreover, those peripheral neurons that are involved in controlling laryngeal movement are common to breathing, swallowing, vocalization, coughing, and sneezing (Shiba et al., 1999). It is possible that the neural networks are shared, to some extent, between multiple functions and that these shared neurones ‘switch’ between these functions (Shiba et al., 1999).

The precise pattern of BSC may be determined by a complex interaction of multiple neural networks in the brainstem, influenced by descending cortical input. Determining the site and nature of the interaction of these networks is difficult for two reasons. First, respiration and swallowing share peripheral innervation - the hypoglossal motoneurones (Popratiloff et al., 2001), glossopharyngeal sensory neurones (Kiernan, 1998; Perlman & Christensen, 1997), and the vagus motor and sensory neurones (Figure 2.7) (Perlman & Christensen, 1997; Rontal & Rontal, 1976) - and, thus, it is difficult to study the neural circuitry of either function in isolation (Sawczuk & Mosier, 2001). Second, determining the sites specifically involved in the two phenomena is beyond the temporal resolution offered by current neural imaging techniques as discussed earlier. For instance, the onset of swallowing and the onset of SA do not occur at exactly the same time (Martin-Harris et al., 2003) but within a short timeframe, as little as 30 ms (Klahn & Perlman, 1999). As “the occurrence of swallowing at specific points

in the respiratory cycle indicates the site of potential interaction of the swallowing and breathing central patterns generators" (Dick et al., 1993, p. 727), behavioural investigation of the interaction between breathing and swallowing can provide useful insight into neural networking.

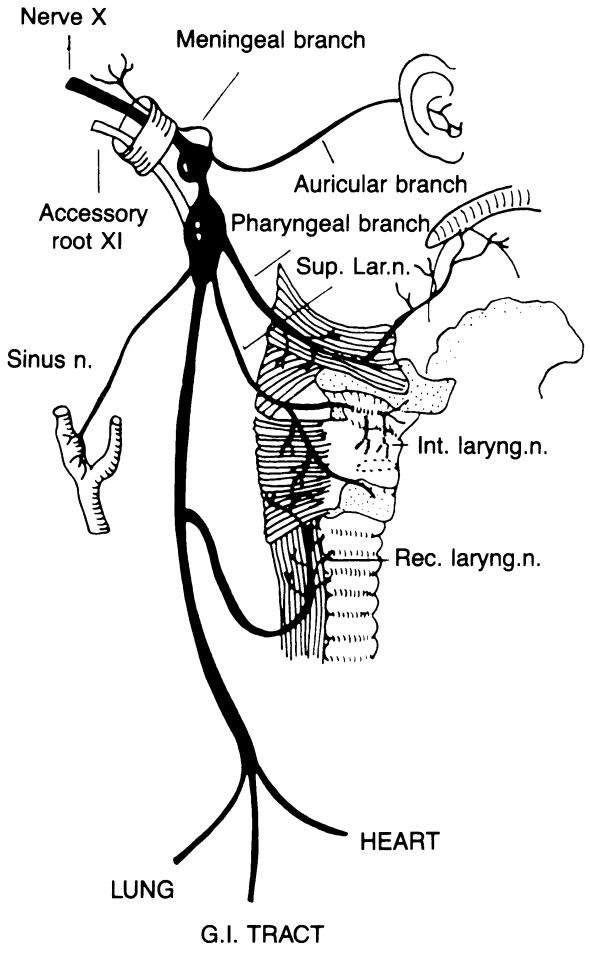


Figure 2.7 The innervation of the vagus nerve of the muscles involved in swallowing and respiration. From Rontal, M., & Rontal, E. (1976). Lesions of the vagus nerve: diagnosis, treatment and rehabilitation. The Laryngoscope, 87(1), 72-86.

It is clear that, in animals, the brainstem is predominantly involved in BSC. Whether the same applies to humans is unknown. The impact of swallowing on respiratory patterns demonstrated in neurologically intact species are also observed in decerebrate animals (Dick et al., 1993; Miller & Sherrington, 1916), implying that the interaction between respiration

and swallowing is preserved in the absence of cortical input (Paydarfar et al., 1995). Intracellular analysis of the firing patterns of animal brainstem neurones supports this. The distribution and firing patterns of the respiratory and swallowing-related neurons in the NTS of the rat suggest that these neurones are involved in the 'initiation, pattern formation and mutual inhibition between swallowing and respiration' (Saito et al., 2002, p. 1047).

Numerous other brainstem sites may be involved in BSC: areas around the NA such as the intermediate ventral respiratory group (Bianchi et al., 1995), areas lateral to the NTS (Gestreau et al., 2000; Gestreau et al., 1996; Hayashi & McCrimmon, 1996; Larson et al., 1994; Oku et al., 1993; Oku et al., 1994), and areas in the rostral medulla (Feroah, Forster, Fuentes, Wenninger et al., 2002). Feroah et al. (2002) argue that the effects of microinjection of excitatory amino acid receptor agonists and antagonists into the facial, gigantocellularis reticularis, and vestibular nuclei in the medulla of awake goats suggests that these sites are involved in BSC. The injection of one agonist into these three nuclei resulted in an increase in swallowing frequency and respiratory changes. The agonists and one antagonist altered the duration of the respiratory phases and was more profound when injecting the facial and gigantocellularis reticularis nuclei than the vestibular nucleus. The effect also differed for the respiratory phase associated with swallowing suggesting that these nuclei are involved in the interaction of respiration and swallowing (Feroah, Forster, Fuentes, Wenninger et al., 2002). However, none of the injections specifically modified the phase in which swallowing occurred, thus it can be argued that these findings suggest that these nuclei are merely the site of interaction between the neural networks of breathing and swallowing and the control centre of BSC. Feroah et al. (2002) elude to this by stating that the gigantocellularis reticularis nucleus may be the site of 'convergence' of many stimuli, reflecting its integrative role in the coordination of breathing, swallowing, and many other functions such as vomiting and sneezing.

As demonstrated, the neuroanatomy of BSC of mature individuals is not clear. The development of the BSC neural networks is even less clear. Miller (1999) argues that the maturation of the brainstem neural networks (central pattern generators) may account for postnatal changes in mammalian infant BSC. In newborn animals, elicitation of swallowing results in complete cessation of respiration (Harned, Myracle, & Ferreiro, 1978; Lucier, Storey, & Sessle, 1979) but, at 2 - 3 months of age, the elicitation results in the alternation of respiration and swallowing (Harned et al., 1978). It could be argued that by 2 - 3 months of age, descending input from suprabulbar structures may be present given that none of the

animals used in these studies had been decerebrated. Although the brainstem's involvement in BSC is clearly substantial, there is evidence that suggests that the cortex is also involved. During NREM sleep, the phasic activities of pharyngeal and diaphragmatic muscles of healthy adults are altered following momentary electrocortical arousal (Carlson, Carley, Onal, Lopata, & Basner, 1994). Furthermore, a microstimulation study of the adult rat insular cortex identified overlapping respiratory and gastro-motor areas (Aleksandrov, Aleksandrova, & Bagaev, 2000). Stimulation of this particular site resulted in inhibition of breathing and increased gastric tension which suggests that the insula may be involved in the coordination of breathing and gastrointestinal activities (Aleksandrov et al., 2000). Similarly, earlier studies employing microstimulation of the rat insular cortex also reported evoked cardiovascular and gastrointestinal reactions (Ruggiero, Mraovitch, Granata, Anwar, & Reis, 1987; Yasui, Breder, Saper, & Cechetto, 1991).

The specific cortical site influencing BSC may be any of the cortical sites identified as involved in swallowing and/or respiration, such as the insular cortex (Aleksandrov et al., 2000; Stickler et al., 2003), premotor cortex (Colebatch et al., 1991; Mosier & Bereznaya, 2001), motor cortex (Colebatch et al., 1991; Martin et al., 2001), and supplementary motor cortex (Colebatch et al., 1991; Mosier & Bereznaya, 2001). Both breathing and swallowing also activate subcortical sites such as the basal ganglia (Fink et al., 1996; Mosier & Bereznaya, 2001) and thalamus (Davenport & Reep, 1995; Mosier & Bereznaya, 2001), which may indicate pathways through which the cortex interacts with the brainstem to coordinate breathing and swallowing.

Support for cortical involvement in breathing-swallowing organisation is found in the comparison of data obtained from awake participants and data obtained from unconscious or sleeping participants. SA most frequently occurs during the expiratory phase of respiration in awake humans (Hiss et al., 2001; Klahn & Perlman, 1999; Martin et al., 1994; Perlman et al., 2000; Preiksaitis et al., 1992) but, in patients under general anaesthesia, SA occurs just as frequently during inspiration as during expiration (Nishino & Hiraga, 1991). Thus, anaesthetized participants demonstrate increased variability in BSC compared to the more uniform coordination produced by awake participants reported in the literature (Nishino & Hiraga, 1991). The authors suggest that consciousness influences BSC, without explicitly implicating the cerebral cortex. Although the cortical and diencephalic input on the respiratory CPG is minimized by anaesthesia (Neubauer, 1990), the effects of anaesthesia may not be limited to suprabulbar structures. Thus, it is plausible that the global suppression

of brain activity, potentially including brainstem structures, induced by the anaesthetic was, at least in part, responsible for atypical BSC observed by Nishino and Hiraga (1991). It was for this reason that BSC during natural sleep was compared to wakefulness in a recent pilot study (Kelly et al., in press). Although this pilot study also showed decreased variability in BSC when cortical activation is heightened (i.e., during wakefulness), the role of the cortex remains speculative given methodological flaws discussed later (see section 2.4.3.2).

Further support for the role of the cortex in BSC is evident in the comparison between animal and human studies. Research using both anaesthetized (Doty & Bosma, 1956; Kawasaki, Ogura, & Takenouchi, 1964) and unanaesthetized animals (Feroah, Forster, Fuentes, Wenninger et al., 2002; Kawasaki et al., 1964; McFarland & Lund, 1993) has shown that post-swallow inspiration occurs more frequently in animals than in adult humans. The large majority of spontaneous swallows in adult goats (Feroah, Forster, Fuentes, Lang et al., 2002) and dogs (Kawasaki et al., 1964) are followed by inspiration whereas swallows preceding inspiration are uncommon in human adults (Hirst et al., 2002; Hiss et al., 2001; McFarland & Lund, 1995; Paydarfar et al., 1995; Preiksaitis et al., 1992; Shaker et al., 1992). It is well established that the cerebral cortex is more developed in humans than animals (Gottesmann, 2004), thus the differences in BSC between humans and animals may be a reflection of a relatively underdeveloped cerebral cortex. Although this argument is tenuous since brainstem differences may also account for the inter-species difference, it is worth considering.

There is some evidence that the cerebellum may also influence BSC. Like several sites in the cerebral cortex, MRI studies have shown that the cerebellum is involved in breathing (Gozal et al., 1994) and swallowing (Mosier & Bereznaya, 2001), although its exact role in either function is unclear. The importance of cerebellar functioning for survival is emphasized by speculations of potential cerebellar involvement in SIDS (Cruz-Sanchez et al., 1997; Harper, Woo, & Alger, 2000). The results of histological examination of the cerebellar cortices of SIDS victims suggest that delayed cerebellar development may contribute to SIDS given the role of the cerebellum in moderating cardiopulmonary functions (Cruz-Sanchez et al., 1997). Discrete lesions to the cerebellum as a result of the removal of a neoplasm may result in apnoea, hypoventilation and/hypoxemia in children (Chen et al., 2005). Interestingly, approximately half of those children who demonstrated pathological apnoea also presented with dysphagia (Chen et al., 2005). Dysphagia in these children may reflect bulbar damage as a result of the surgery (Chen et al., 2005), however since bulbar damage in all these children was not confirmed, the concurrent breathing and swallowing dysfunction may reflect the role

of the cerebellum in the moderation of breathing and swallowing and, therefore, potentially BSC.

Cerebellar nuclei are involved in increasing ventilation (resulting in increased respiratory rate or tidal volume) and coughing (review by Xu & Frazier, 2002). Little is known about the role of the cerebellum in swallowing. Mosier (2001) hypothesized that the cerebellum may be involved in the adaptive modulation of the swallowing response (in particular the tongue and pharyngeal muscles) based on sensory input. The results of a PET study of volitional swallowing in healthy adults suggests that the cerebellum is more likely to be involved in the pharyngeal than the oral stage of swallowing (Zald & Pardo, 1999). Zald and Pardo suggest that "the cerebellum may help to control the coordination, sequencing, and timing of swallowing" (1999, p. 285). These hypotheses are supported by the role of the cerebellum in integrating sensory input and motor output (review by Apps & Garwicz, 2005), but also its role in timing and motor coordination (Shannon et al., 2004) or the adaptation of motor coordination (review by Thach, Goodkin, & Keating, 1992). Thus, it is conceivable that the cerebellum may, too, contribute to BSC.

In summary, there is unequivocal evidence that brainstem contains the neurones at least predominantly responsible for the initiation and execution of the BSC motor sequence, and must, in turn, contain the 'blueprint' for the precise pattern of BSC. Suprabulbar and cerebellar influences are more subtle and research has yet to conclusively prove their existence.

2.3 The Biomechanics of Swallow Apnoea and Breathing-Swallowing Coordination

In order to describe the patterns of BSC, simultaneous recordings of respiration and swallowing are required. Swallowing is typically detected by an increase in submental muscle activity, measured by SEMG (Klahn & Perlman, 1999; Martin et al., 1994; Preiksaitis & Mills, 1996; Shaker et al., 1992; Smith et al., 1989; Yamamoto & Nishino, 2002). Occasionally SEMG is used in combination with pharyngeal acoustics (Preiksaitis & Mills, 1996) or electroglottography (Klahn & Perlman, 1999). In order to determine the phase of respiration or to detect SA, researchers have used nasal cannulas (Klahn & Perlman, 1999; Preiksaitis et al., 1992; Selley, Flack, Ellis, & Brooks, 1989a; Selley et al., 1989b; Selley,

Flack, Ellis, & Brooks, 1990), nasal thermistors (Mizuno & Ueda, 2003; Selley, Ellis, Flack, & Brooks, 1990), and respiratory plethysmography (Martin et al., 1994; Preiksaitis & Mills, 1996). Respiratory tracings obtained at the nostril without chest/abdominal wall transducers are considered adequate for detecting apnoea in infants (Hanlon et al., 1997).

Swallowing apnoea was documented as early as 1920 (Clark, 1920) and reported by many authors subsequently (Doty & Bosma, 1956; Martin et al., 1994; McFarland & Lund, 1993, 1995; Miller & Sherrington, 1916; Nishino et al., 1985; Preiksaitis et al., 1992; Smith et al., 1989; Sumi, 1967). SA is the result of biomechanical closure of the upper airway during swallowing and the cessation of respiratory efforts. Biomechanical closure consists of a three-tiered system that is activated during swallowing: arytenoid-to-epiglottis contact, closure of the true, and closure of the false vocal folds (Miller, 2002). Supraglottic closure (defined as full epiglottic deflection) occurs on average between 0.7 s and 1 s before the bolus reaches the UOS (Kendall, Leonard, & McKenzie, 2004) and may be the cause of the brief inspiration called the ‘schluckatmung’ or ‘swallow breath’ that has been associated with swallowing (Zwaardemaker, 1905 cited by Wilson et al., 1981). Although the timing of swallow-induced glottic closure is highly variable (Ohmae, Logemann, Kaiser, Hanson, & Kahrilas, 1995), laryngeal closure (Jafari, Prince, Kim, & Paydarfar, 2003; Medda et al., 2003) and prompt, rapid laryngeal elevation (Kahrilas, Lin, Rademaker, & Logemann, 1997) avert aspiration. The onset of glottic closure precedes the onset of hyoid bone movement, base of tongue movement, and submental SEMG activity by approximately 0.3 s (Shaker, Dodds, Dantas, Hogan, & Arndorfer, 1990).

In adults, the cessation of respiratory efforts begins between 0.03 s (Klahn & Perlman, 1999; Martin et al., 1994) and 1.04 s (Martin et al., 1994) before the onset of hyolaryngeal excursion (Paydarfar et al., 1995), or at least no later than at the onset of SEMG activity (McFarland & Lund, 1995). More specifically, SA is typically initiated before the onset of the hyoid bone elevation (which is the main contributor to epiglottic deflection) (Martin-Harris et al., 2005) and between 0.02 s (Klahn & Perlman, 1999) and 0.19 s before laryngeal elevation (Martin et al., 1994). SA begins approximately 0.28 s after the onset of swallow-associated submental SEMG activity (Martin et al., 1994). In general, SA typically begins prior to the ingested bolus having entered the hypopharynx and the initiation of the pharyngeal stage of swallowing: a mechanism which likely serves to prevent aspiration in human adults (Palmer & Hiiemae, 2003).

SA ends when post-swallow respiration resumes during the descent and reopening of the larynx (Martin et al., 1994; Martin-Harris et al., 2003) and, relative to the onset of laryngeal descent, SA termination is largely consistent across varying discrete bolus volumes (Martin et al., 1994). At this point the ingested bolus tail has reached the oesophagus (Palmer & Hiiemae, 2003).

Evidence for the central component of SA is provided by respiratory plethysmography recordings which indicate that the movement of thoracic walls is halted during SA in adult humans (Martin et al., 1994; Preiksaitis & Mills, 1996; Smith et al., 1989). Furthermore, laryngectomized (Hiss et al., 2003) and intubated patients (Nishino & Hiraga, 1991), in whom laryngeal closure cannot occur, also exhibit SA.

In human neonates the closure of the vocal folds (glottis) during nutritive swallowing was confirmed radiographically in the 1950s (Ardran, Kemp, & Lind, 1958). Despite this, it appears that until the 1980s, it was accepted thought that human infants could breathe and swallow simultaneously (e.g., Laitman, Crelin, & Conlogue, 1977; Negus, 1949; Peiper, 1963; Polgar & Weng, 1979). More recent research in human infants has confirmed the existence of SA in human term and preterm infants (Bamford et al., 1992; Jeffery, Ius, & Page, 2000; Stevenson & Allaire, 1991; Thach & Menon, 1985; Weber et al., 1986; Wilson et al., 1981). However some authors have observed continued respiratory efforts during swallowing in infants, confirmed by plethsmography (Wilson et al., 1981). This may be indicative of some “inefficiency of the integration of swallowing and breathing” (Wilson et al., 1981, p. 857). In addition, this perhaps implies that, unlike adults, infant SA is due to biomechanical obstruction rather than the cessation of centrally-governed respiratory efforts. Also, unlike adults, neonates have irregular respiratory patterns characterized by frequent prolonged respiratory pauses (review by Praud & Reix, 2005) during which nutritive and non-nutritive swallowing can occur (Don & Waters, 2003; Lau et al., 2003; Menon, Schefft, & Thach, 1984; Miller & DiFiore, 1995; Wilson, Thach, & Brouillette, 1980; Wilson et al., 1981). In fact, preterm infants swallow mainly during respiratory pauses (Mizuno & Ueda, 2003). Preterm and term infants swallow in succession without breathing between swallows although term infants seldom swallow more than twice during a feeding-related apnoeic interval (Hanlon et al., 1997).

Benign prolonged respiratory pauses or apnoeas can last between 2 s (Curzi-Dascalova & Christova-Gueorguieva, 1983; Hoppenbrouwers et al., 1980) and 15 s (Hoppenbrouwers et

al., 1977) in the normally developing human infant population. There are three types of prolonged respiratory pauses which can be associated with swallowing in human infants: cessation of respiratory efforts (central apnoea), persistence of respiratory efforts in the presence of upper-airway closure (obstructive apnoea), or a combination of the two (mixed apnoea). Specifically, central and obstructive apnoeas are associated with nutritive swallowing (Belgaumkar, 1976; Koenig et al., 1990; Menon et al., 1984) and non-nutritive swallowing in preterm infants (Menon et al., 1984; Wilson et al., 1981) and healthy infants (Miller & DiFiore, 1995; Thach & Menon, 1985). All three types of apnoea are associated with non-nutritive sucking during wake and sleep in preterms (Miller & DiFiore, 1995) and non-nutritive swallowing in preterm and term infants (Don & Waters, 2003). However, data in the latter study (Don & Waters, 2003) were obtained from infants with a history of an apparent life-threatening event, or who had a SIDS sibling, or who required further investigation of pathologic breathing; thus, the distribution of swallows within the three types of apnoeas in healthy term infants remains unknown.

During sleep, there are two patterns of breathing in term infants at birth: apnoeic and periodic breathing (Hoppenbrouwers et al., 1977). Apnoeic breathing is characterized by intermittent protracted respiratory pauses (6 - 15 s), whereas short pauses (3 - 6 s) within a 20 s period defines periodic breathing (Hoppenbrouwers et al., 1977). The frequency of apnoea decreases with increasing age until a plateau is reached at approximately 3 months whereas periodic breathing remains relatively constant during the first 6 months (Hoppenbrouwers et al., 1977). In infants, sleep swallows occur less frequently during phases of periodic breathing than periods of apnoea (Miller & DiFiore, 1995).

For those swallows occurring between prolonged respiratory pauses, the duration of SA lasts approximately 0.67 s for nutritive swallows (Hanlon et al., 1997; Koenig et al., 1990) and approximately 1.0 s for non-nutritive swallows (Wilson et al., 1981). Soon after birth, nutritive swallowing apnoea duration (SAD) is longer for preterm infants than term infants at 760 ms and 672 ms, respectively (Hanlon et al., 1997). However, by term age, the SAD of preterm infants shortened to be no different that of term infants (Hanlon et al., 1997). This occurred regardless of the duration of postnatal feeding experience, thus neural maturation, and not experience appears to be primary determinant of SAD in very early infancy (Hanlon et al., 1997).

The impact of postnatal age on SAD is debatable. A pilot study found no influence of age on SAD (Kelly et al., in press) but others argue that SAD increases with age (Selley et al., 1989a) and that age effects depend on gender and the swallow type (Hiss et al., 2001). Females demonstrate an increase in SAD with age for dry swallows and males a decrease; the opposite is true for bolus swallows for which females demonstrate a decrease and males an increase (Hiss et al., 2001).

The effect of bolus size on SAD may be also age-related. A trend for SAD to increase from 1.06 s to 1.25 s as the bolus size increased from 5 to 20 ml was seen in adults but only for those over 60 years (Hirst et al., 2002). Serial swallowing results in an increase in SAD (Martin et al., 1994) as does the ingestion of a solid bolus compared to semi-solids and liquids (Preiksaitis & Mills, 1996). There appears to be little agreement regarding the impact of smaller discrete bolus volumes. Some authors show no change in SAD between discrete bolus volumes under 20 ml (Martin et al., 1994; Preiksaitis et al., 1992; Preiksaitis & Mills, 1996). More recent research, including greater numbers of participants, demonstrate shorter SAD for the swallowing of boluses under 10 ml than for 20 - 25 ml (Butler, Postma, & Fischer, 2004; Hiss et al., 2001). There is consensus however, that the mere presence of a bolus results in a decrease in SAD as evident in the comparison of dry and nutritive swallows (Miyazaki, Yamashita, & Komiyama, 1994; Preiksaitis et al., 1992; Shaker et al., 1992). This indicates that the neural controls of SAD respond to afferent information during swallowing.

2.4 Phase of Respiration in which Swallowing Occurs

It was originally suggested that a swallow would be executed entirely within a single phase of respiration (Clark, 1920). Subsequent research, however, indicated that swallow-associated brainstem respiratory neuron activity is invariant and not dependent on the phase in which swallowing was initiated (Sumi, 1963). More recent behavioural research indicates that BSC in healthy individuals is indeed altered by numerous internal and external variables (Kelly et al., in press; McFarland, Lund, & Gagner, 1994; Nishino & Hiraga, 1991; Nishino et al., 1985; Preiksaitis et al., 1992; Shaker et al., 1992). These variables include posture or body position, level of arousal or consciousness, age, nature of the swallowing task, and ingestion of solid or liquid boluses.

2.4.1 Effect of Body Position

Research has identified physiological and biomechanical effects of body position on respiration and swallowing in healthy adults, although information on infants is scarce. Similarly, body position may indirectly influence BSC, although research on this is minimal and conflicting. Whatever, body position is an important variable to consider in the design of future BSC studies.

2.4.1.1 Body Position and Respiration

Evidence for the effect of body position on the respiration of infants stems largely from research evaluating SIDS. In a review of the SIDS literature it was stated that "the majority of findings suggest a reduction in physiological control related to respiratory, cardiovascular, and autonomic control mechanisms, including arousal during sleep in the prone position" (Galland, Taylor, & Bolton, 2002, p. 332). In the prone position, the frequency of swallowing in response to infusion of liquid into the pharynx, respiratory rate, and frequency of arousal is less in prone than in supine position in healthy term neonates (Jeffery, Megevand, & Page, 1999). The former phenomenon paired with reduced rate of respiration without associated increase in arousal suggests reduced airway protection in the prone position (Jeffery et al., 1999). The prone position compromises some aspects of healthy infant lung function such as peak expiratory flow rate and crying vital capacity when compared to supine (Shen, Zhao, Huang, Lin, & Wu, 1996). This may be due to detrimental effects of the prone position on lung volume and upper-airway resistance (Shen et al., 1996).

In adults, there is considerable evidence that the effect of body position on ventilation is most apparent between vertical and horizontal positions. Forced vital lung capacity and forced expiratory volume are less in the horizontal position than in vertical position in healthy individuals (Manning, Dean, Ross, & Abboud, 1999). Lung volume and expiratory reserve volume are less in the side-lying compared to the upright position (Behrakis, Baydur, Jaeger, & Milic-Emili, 1983). Expiratory reserve volume is also less in the supine position compared to the upright and side-lying positions (Behrakis et al., 1983).

These position-related effects of respiration may be attributed to biomechanical forces since the biomechanics of breathing differ between upright and supine body positions (review by Hoit, 1995). Changes in body position result in changes in the degree of abdominal compression of the lungs, particularly in the supine position and to a lesser extent in the side-

lying position, which in turn influences lung function (Hough, 1984). Expiration is achieved by recoil forces in supine but in the upright position abdominal muscles facilitate expiration (review by Hoit, 1995). Abdominal muscles are active during the entire respiratory-phase cycle, preventing the distension of the abdomen and maintaining adequate diaphragmatic tension (review by Hoit, 1995). The contribution of the abdomen in the upright position may explain why maximal expiratory pressure is higher in the sitting position than in supine and side-lying (Badr, Elkins, & Ellis, 2002). This positional effect on the maximal expiratory pressure may also be the result of differing expiratory reserve volume and lung compliance, both of which are greater in the sitting upright position than in supine and side-lying (Behrakis et al., 1983). Furthermore, air flow resistance is lower in the upright than the supine and side-lying positions which may reflect a position-related change to upper airway resistance (Behrakis et al., 1983).

Thorough analysis of respiratory function in the side-lying position in healthy individuals has demonstrated that forced expiratory volume and lung capacity are less when the side-lying position is adopted than when sitting upright (Manning et al., 1999). A decrease in expiratory volume may be the result of reduced respiratory recoil mechanisms or greater airway obstruction whereas a decrease in lung capacity may be the result of the effects of gravity on circulation and the effect of visceral and subsequent diaphragmatic displacement (Manning et al., 1999). This is supported by the suggestion that side-lying may permit abdominal but not thoracic distension, particularly on the underside, which may account for decreased lung volumes (Badr et al., 2002). These biomechanical forces and lung function that change between upright and side-lying positions may also subtly and indirectly influence BSC.

2.4.1.2 Body Position and Swallowing

There is less evidence for a body position effect on swallowing biomechanics relative to the abundance of respiratory-related research. General body posture (Castell, Dalton, & Castell, 1990; Johnsson, Shaw, Gabb, Dent, & Cook, 1995) and even the specific position of the head and neck (Ekberg, 1986) influence swallowing biomechanics. The transit time of thin liquids through the pharynx is shorter in the upright than the horizontal body position (Ingervall & Lantz, 1973). Body position alters the dimensions of UOS opening (Johnsson et al., 1995) and the timing of maximal UOS relaxation relative to pharyngeal contraction; this is increased in the upright compared to supine position (Castell et al., 1990). The distal oesophagus also behaves differently between vertical and horizontal positions (Chang, Lee, Yeh, & Lee,

1996). In the horizontal position, contraction pressure is higher and contractile intervals are longer during swallowing but lower oesophageal sphincter resting pressure is reduced (Chang et al., 1996).

2.4.4.3 Body Position and Breathing-Swallowing Coordination

There are no studies that have directly examined the effects of body positioning and posture on the BSC of infants, and studies of such in adults are few but suggest that not all positions influence BSC.

Support for a possible body position effect on the BSC of infants arises from numerous sources. First, baroreceptor reflexes are present at birth and are responsible for cardiovascular changes occurring with a change in body position (Chen, Tsai, & Lan, 1995). Second, the link between the prone position and SIDS highlights the impact of body position on infant physiology (Hauck et al., 2003; Jeffery et al., 1999; Tuladhar, Harding, Cranage, Adamson, & Home, 2003). Third, infants sleep for shorter periods, demonstrate longer periods of rapid-eye-movement (REM) sleep, have more frequent arousals (Vandenplas & Hauser, 2000), and breathe faster (Jeffery et al., 1999) in the supine than in the prone position. Finally, there are differences in EEG recordings between the prone and supine positions in healthy sleeping infants (Horne, Egodagamage, Cranage, & Adamson, 2003).

In adults, the effect of body position on BSC is debatable. McFarland et al. (1994) evaluated standing upright compared to resting on hands and knees (quadruped) and found that SA occurred later in the expiratory phase in the former than the latter position. In both conditions, SA occurred predominantly in the expiratory phase, but the implication of the precise location of SA within the expiratory phase is unclear. On the other hand, Shaker et al. (1992) found no difference in BSC between sitting and supine. Further research is required to confirm the effect of body position on BSC in positions such as side-lying and prone. Given the physiological and biomechanical effects of body positioning on certain features of respiration and swallowing in healthy individuals the potential effect of body position on BSC should be further investigated.

In summary, there are documented biomechanical and physiological effects of body position on respiration and swallowing, although the impact of body position specifically on BSC is unknown for infants and minimally established in adults.

2.4.2 Effect of Level of Arousal

Before the impact of level of arousal on respiration, swallowing, and BSC can be fully appreciated, understanding of the neurophysiology of sleep is imperative.

2.4.2.1 The Neurophysiology of Sleep

Wakefulness is a state of substantial cortical disinhibition (Gottesmann, 2004). Sleep, on the other hand, is "a physiologic state of relative unconsciousness and inaction of the voluntary muscles" (Pugh, 2000, p. 1648). Sleep can be categorized into two broad behavioural states: rapid eye movement (REM) and non-rapid eye movement (NREM). The paediatric equivalent of REM sleep is referred to as 'active sleep' and NREM sleep is referred to as 'quiet sleep' (Kahn et al., 2000). Unlike adults, however, human infants also exhibit 'indeterminate sleep' which is neither an active nor a quiet sleep state, but an electrophysiological sleep state nonetheless (Curzi-Dascalova & Christova-Gueorguieva, 1983; Don & Waters, 2003; Ellingson, Peters, & Nelson, 1982; Hoppenbrouwers, Hodgman, Arakawa, Geidel, & Sterman, 1988; Hoppenbrouwers et al., 1977). REM sleep is characterized by eye movements and cortical activation and is associated with dreaming (Nofzinger, Mintun, Wiseman, Kupfer, & Moore, 1997). NREM sleep is a sleep state that is not associated with eye movements or dreaming (Siegel, 2004), but, although cortical activity is less during NREM, it is not completely subdued (Hofle et al., 1997). Despite the abundance of sleep research, there is still much to be learned about the functional neuroanatomy and purpose of sleep (Maquet, 2000) and this appears to be particularly true for infant sleep given the apparent relative paucity of paediatric sleep literature. Nonetheless, research has shown that the specific sites and degree of cortical activation differs markedly between NREM sleep, REM sleep, and wakefulness. The latter two appear to exhibit activation of similar CNS sites but not necessarily to the same degree. These patterns of activation and relative 'deactivation' during sleep are outlined below according to the results of EEG and PET studies.

The most common tool in sleep research is electroencephalography (EEG), which detects the electrical rhythms generated by cortical and subcortical systems (Hobson & Pace-Schott, 2002). The EEG signals obtained during REM sleep are indicative of increased firing rates of the reticular formation, thalamocortex, and cortex (Steriade & McCarley, 1990). High frequency, low amplitude (desynchronized) EEG activities, rapid eye movement, and low

muscle tone are observed during REM sleep (Muzur, Pace-Schott, & Hobson, 2002). Higher amplitude, low frequency (synchronized) EEG wave activity reflects NREM sleep which may be further categorized into four stages depending on the 'depth' of sleep (Pace-Schott & Hobson, 2002). Slow oscillating (<1 kHz) EEG spindles and delta waves are characteristic of deep sleep (Steriade, Nunez, & Amzica, 1993). The slow oscillations appear to be primarily the result of changes at the cellular level: specifically, Contreras et al. propose "disfacilitation to be the dominant mechanism in the membrane of cortical and thalamic cells during the spontaneous long-lasting hyperpolarizations" (1996, p. 251). Awakening from sleep entails cortical desychronisation and activation (Akerstedt et al., 2002).

The alternating NREM-REM sleep cycle in adult humans occurs four or five times during a night with an increase in the proportion of REM to NREM sleep as the night progresses (Pace-Schott & Hobson, 2002). Infants may fall immediately into REM sleep from wakefulness or soon thereafter (review by Sadeh, 2000) without going through a substantial NREM sleep stage like adults. Moreover, neonates dedicate a greater proportion of sleep to REM than adults (Curzi-Dascalova & Challamel, 2000; Hobson, 1989), which decreases rapidly in the first year of life until it approximates that of an adult between the ages of 2 and 6 years (Curzi-Dascalova & Challamel, 2000) or as late as the age of 10 (Hobson, 1989).

The brainstem and diencephalon are important structures involved in the NREM-REM cycling (Pace-Schott & Hobson, 2002). Given the reciprocal connection between these structures and the cortex, it is possible that descending cortical input influences the behavioural profile of sleep (Pace-Schott & Hobson, 2002). Ascending neuronal information from the arousal systems including the reticular activating system, and diencephalic structures such as the hypothalamus and the basal forebrain (ventral telencephalon) are responsible for initiating REM sleep and wakefulness (Braun et al., 1997; Hobson & Pace-Schott, 2002) and suppressing the slow oscillation, spindles, and delta rhythms of NREM sleep (Hobson & Pace-Schott, 2002). The ascending neural transmission from the reticular formation to the cortex occurs through dorsal and ventral ascending systems directly via the corticoreticular pathways (which stem from the primary motor and premotor cortices, Hallett, 2002) or via projections to the basal ganglia, thalamic nuclei, or basal forebrain (review by Braun et al., 1997). The basal ganglia, through which the ascending reticular information passes en route to the cortex, may be the gating mechanism that regulates cortical activity (review by Braun et al., 1997).

In the transition from NREM to REM sleep, a cortico-subcortical connection appears to be established between the neocortex (post-rolandic sensory cortex) and the sensory relay nuclei in the thalamus (Braun et al., 1997). This ‘coupling’ of cortical and subcortical sites may be that which distinguishes NREM from REM sleep and wakefulness (Braun et al., 1997). The only feature shared by REM and NREM sleep may be the deactivation of the orbital, dorsolateral prefrontal, and inferior parietal cortices which is the essential distinguishing feature of sleep (Braun et al., 1997). This is echoed by the postulation that one of the main differences between sleep and wake is the level of activity of the fronto-parietal network, which is more active during wakefulness than sleep (Maquet, 2000).

The literature indicates that cerebral activity during NREM sleep is less than REM sleep (Madsen et al., 1991) and wakefulness (Braun et al., 1997; Maquet, 2000). More specifically, “widespread deactivation characterizes the wake-to-NREM-sleep transition, whereas selective reactivation is seen in REM sleep” (Hobson & Pace-Schott, 2002, p. 691). There is a dramatic deactivation of the frontoparietal association areas and preservation of activity in the primary and secondary sensory cortices during NREM (Braun et al., 1997). REM sleep, on the other hand, “may constitute a state of generalized brain activity with the specific exclusion of executive systems which normally participate in the highest order analysis and integration of neural information” (Braun et al., 1997, p. 1190). REM sleep is characterized by selective reactivation of the medial and posterior prefrontal regions in humans (review by Muzur et al., 2002).

The following sites exhibit a reduction in regional cerebral blood flow and/or energy metabolism during NREM relative to REM and wakefulness according to two comprehensive literature reviews (Hobson & Pace-Schott, 2002; Maquet, 2000): the brainstem (particularly the pons), cerebellum, thalamus, hypothalamus, basal ganglia (particularly the caudate nucleus), the lateral and medial regions of the prefrontal cortex, anterior cingulate cortex, precuneus, and the mesial aspect of the temporal lobe. It is likely that the deactivation, as indicated by minimal blood flow in the brainstem during sleep, permits the production of sleep (Maquet, 2000). The relative reduction of cerebellar activity during NREM sleep results in decreased sensorimotor function and the relative increased threshold for arousal during deep NREM stages may be a reflection of the cessation of the ascending information from the reticular formation which is characteristic of NREM sleep (Braun et al., 1997).

The functional neuroanatomy and neural interactions for NREM sleep, REM sleep, and wakefulness differ (Maquet, 2000), yet the degree of cerebral metabolism during REM sleep and waking are similar (Maquet, 1995). In fact, the level of activity in the hippocampus, parahippocampal and medial prefrontal cortices, and the anterior insula is greater during REM sleep than in pre-sleep wakefulness (Maquet, 1995). The following sites are activated during REM: the pons, midbrain, thalamus, hypothalamus, basal ganglia, the medial limbic-related cortices (review by Hobson & Pace-Schott, 2002) such as the amygdaloid complexes, hippocampal formation (Maquet, 2000), lateral hypothalamic area, amygdaloid complex, septal-ventral striatal areas, and infralimbic, prelimbic, orbitofrontal, dorsolateral prefrontal cortex, anterior and posterior cingulate cortex (Hobson & Pace-Schott, 2002; Maquet, 2000; Nofzinger et al., 1997), entorhinal and insular cortices (Nofzinger et al., 1997), and the cerebellar vermis (Braun et al., 1997). In contrast, Nofzinger et al. (1997) reported that there are only a few scattered unspecified areas of relative deactivation during REM sleep. In summary, the primary sites involved in REM sleep are the brainstem and cortex, whereas the thalamus, subcortex, and neocortex are primarily involved in NREM sleep (review by Curzi-Dascalova & Challamel, 2000).

2.4.2.2 Effect of Level of Arousal on Breathing-Swallowing Coordination

Given the dramatic differences in CNS activation between sleep states, it is not surprising that level of arousal affects the frequency of swallowing (Kahrilas et al., 1987; Lear, 1965; Lichter & Muir, 1975; Sondheimer, 1989) and respiratory patterns (Gozal & Harper, 2000; Mador & Tobin, 1991) in infants and adults. Level of arousal also affects BSC in human adults (Kelly et al., in press; Nishino & Hiraga, 1991) but its impact on the BSC of infants is unknown as no research has compared the BSC of sleeping and awake infants.

Cortical activation during REM sleep and wakefulness may contribute to the changes in respiration and swallowing. In summary, a global deactivation characterizes the transition between waking and NREM sleep followed by selective reactivation of the medial and posterior prefrontal regions during REM sleep (review by Muzur et al., 2002). Essentially, there is a decrease in cerebral activation during sleep but particularly in the fronto-parietal (Maquet, 2000) and prefrontal cortex, the latter being involved in executive functions (Braun et al., 1997). Sleep dampens the higher CNS, which inhibits pharyngeal activity (Isono, 2000). More specifically, “sleep either reduces the sensitivity of sensory receptors, dampens swallowing centre sensitivity to sensory information, or inhibits motor activity to muscles

involved in swallowing" (Issa, 1994, p. 654). Thus, it is not surprising that during sleep, in the absence of reflux, swallowing rate is dependent on sleep-state in humans of all ages (Don & Waters, 2003; Jeffery et al., 2000; Lear, 1965; Sondheimer, 1989) and animals (Reix et al., 2003; Rigatto, Moore, & Cates, 1986), with an increase in swallowing frequency with arousal (Lear, 1965).

In sleeping infants, the frequency of swallowing associated with prolonged respiratory pauses is highest during active sleep (Don & Waters, 2003). Don and Walters (2003) postulated that this association is the result of the stimulation of the laryngeal chemoreflex (LCR). Swallowing is a key element of the LCR (Praud & Reix, 2005). Reix et al. (2003) suggest that this sleep-state association cannot be due to the stimulation of the LCR by accumulated pharyngeal secretions since saliva production is not influenced by specific sleep state (Gemba, Teranaka, & Takemura, 1996). Instead, two other mechanisms may be at play. First, saliva may not be the stimulus; approximately 22% of apnoeas in preterm infants are associated with gastroesophageal reflux (Menon et al., 1984) which may trigger swallowing (Miller & DiFiore, 1995). This is supported by evidence that acid infusion into the distal oesophagus in sleeping adults results in an increase in the frequency of swallowing more so than water infusion (Orr, Johnson, & Robinson, 1984). Second, increased frequency of swallowing is associated with increased arousal in the presence of acid stimulus which implies that "the primary peristaltic complex results from a volitional act under the control of higher cortical functions" (Orr et al., 1984, p. 818). This is supported by evidence of increased cortical activation during REM than NREM sleep in adults (Muzur et al., 2002). It is therefore possible that heightened cortical activation during REM sleep triggers swallowing and may also explain the higher rate of swallowing in REM than in NREM sleep in mammalian infants (Jeffery et al., 2000; Page et al., 1995; Reix et al., 2003).

Reix et al. (2003) postulated that the bursts of non-nutritive swallowing occurring during apnoeic periods in infants are the result of an inhibitory influence of breathing on swallowing; when respiration ceases, swallowing is triggered. This may occur if the central neural circuitry ensures mutual exclusivity of these two behaviours (Miller & DiFiore, 1995). These theories are problematic for two reasons. First, swallowing does not always coincide with prolonged respiratory pauses (Don & Waters, 2003; Jeffery et al., 2000; Miller & DiFiore, 1995). Second, swallowing occurs soon after the cessation of respiration (< 3 s) in 58% of apnoeic intervals (Miller & DiFiore, 1995). If these behaviours were mutually exclusive, the onset of swallowing would consistently occur at the onset of respiratory pauses. These characteristics

of swallowing-respiration interactions suggest that it is more likely that immature interaction between CPGs in the brainstem is unpredictable rather than being reciprocally inhibitive.

Compared to NREM sleep, respiration during REM sleep is more variable (Mador & Tobin, 1991), and more closely associated with apnoeas in infants (Curzi-Dascalova & Christova-Gueorguieva, 1983; Don & Waters, 2003; Gabriel, Albani, & Schulte, 1976; Hoppenbrouwers et al., 1977). It is thought that cortical information processing may account for the sleep-state effect on respiratory patterns (Sako et al., 2001) and that descending input into the automatic control of breathing is altered by sleep state (Gozal & Harper, 2000).

The effect of sleep state on BSC is evident in newborn lambs born at term. In general, BSC in sleep and wake is highly variable with proportional distribution of swallows of: 37% II, 20% IE, 8% EE, and 35% EI (Reix et al., 2003). However, there were differences between quiet and active sleep and between quiet sleep and wakefulness. There were lower proportions of IE during quiet sleep than during active sleep and wakefulness, lower proportions of II during quiet sleep than during active sleep, and lower proportions of EI during quiet sleep than during wakefulness. These data suggest that the centres controlling sleep have some impact on those responsible for BSC (Reix et al., 2003). However, confirmation of this effect in human infants is yet to be completed. Wilson et al. (1981) monitored BSC in nine preterm infants during sleep and wakefulness but did not compare patterns of BSC between these two conditions.

In human adults, there appears to be consensus that BSC is more variable during sleep or unconsciousness than during wakefulness (Kelly et al., in press; Nishino & Hiraga, 1991). Under anaesthesia, swallows in categories similar to II and EE swallows are equally prevalent (Nishino & Hiraga, 1991), as opposed to the predictable EE pattern in awake individuals (Clark, 1920; Hiss et al., 2001; Kelly et al., in press; Klahn & Perlman, 1999; Martin et al., 1994; Perlman et al., 2000; Preiksaitis et al., 1992; Preiksaitis & Mills, 1996; Smith et al., 1989). Nishino and Hiraga did not provide specific values for those swallows occurring at the respiratory-phase cusps (IE and EI). Instead, they classified these swallows (approximately 6% of the total number of swallows) as ‘undefined’ and did not submit them to further analysis. The application of these data to the healthy population is problematic for two reasons. First, their participants were intubated and, second, sleep was anaesthesia-induced. Endotracheal tubes alter swallowing and respiratory reflexes with the prolonged presence of an endotracheal tube adversely affecting the swallowing reflex (de Larminat, Montravers,

Dureuil, & Desmonts, 1995). Endotracheal tube placement also alters airway reflex responses (Hasegawa & Nishino, 1999). Since the effect of anaesthesia may not be limited to suprabulbar structures, it is difficult to specify what neurophysiological change accounted for these highly variable BSC patterns.

A recent pilot study demonstrated that, during natural sleep, there is a higher proportion of IE swallows and a lower proportion of EE swallows compared to wakefulness (Kelly et al., in press). The decreased variability of BSC during wakefulness in the pilot study suggests that conscious cortical influences may play a substantial role in organizing swallowing-respiratory behaviours and thereby facilitating airway protection (Kelly et al., in press). Unfortunately, there were three independent variables that may have influenced the BSC of the participants in the pilot study. First, the participants' body position differed between the conditions which is problematic given that body position alone may alter BSC (McFarland et al., 1994). Second, liquid swallows were included in the wake but not the sleep condition; sensory input from the liquid bolus may be sufficient to alter the respiratory-swallow pattern (Preiksaitis et al., 1992). Third, objective confirmation of sleep status was not obtained. Thus, the impact of sleep on BSC of healthy infant and adult humans has yet to be definitively determined.

2.4.3 Effect of Age

2.4.3.1 Breathing-Swallowing Coordination in Infants

Swallowing behaviour begins before birth in humans (Miller, Sonies, & Macedonia, 2003; Wolfson & Laitman, 1990) and animals (Harding, Bocking, & Sigger, 1986; Harding, Bocking, Sigger, & Wickham, 1984; Rigatto et al., 1986), as do breathing movements in humans (Cajal, 1996; Cooper, Mahony, Bowie, Albright, & Callen, 1985; Miller et al., 2003) and animals (Harding et al., 1986; Harding, Sigger, Wickham, & Bocking, 1984; Maloney et al., 1975). Even laryngeal contractions have been observed using ultrasound in foetuses as young as 15 weeks gestational age, however, glottic closure does not accompany all foetal swallows (Miller et al., 2003). Continued foetal diaphragmatic movement during glottic closure (Cajal, 1996; Cooper et al., 1985) suggest that these movements are possibly prephonatory activities (Cajal, 1996). Miller et al. (2003) found that foetal diaphragmatic movement and glottic closure do not always coincide. Whether this phenomenon represents the incomplete development of the central component to SA that has been alluded to in neonates (Wilson et al., 1981) is unknown. Furthermore, pre- and post-swallow patterns of human foetal respiratory activity are unknown, however, in foetal sheep, the beginnings of

what becomes BSC after birth are observed in the last third of the gestation period (Harding, Sigger, Poore, & Johnson, 1984). Diaphragmatic activity is inhibited by swallowing during inspiratory activity (Harding, Sigger, Poore et al., 1984). Following birth, swallowing, respiration, and the coordination of the two undergo substantial maturational change but the precise age at which infant patterns of BSC resemble that of adults remains unknown.

In humans, breathing changes throughout infancy and adolescence (Rosen, 2000). These changes are characterized by a decrease in respiratory rate (Gagliardi & Rusconi, 1997; Litscher, Pfurtscheller, Bes, & Poiseau, 1993), and a decrease in the number of respiratory pauses (Hoppenbrouwers et al., 1980; Hoppenbrouwers et al., 1977) except those over 10 s which may actually increase during childhood (Fukumizu & Kohyama, 2004).

Temporal relationships between breathing, swallowing, and tongue movements also undergo maturation. This maturation depends on the gestational maturity of the infant and not the extent of sucking experience (Bu'Lock, Woolridge, & Baum, 1990). Using ultrasound, Bu'Lock et al. observed 'fragmentary' tongue movements, particularly during non-nutritive sucking, in preterm infants at 33 and 34 weeks (gestational age) which were not as evident in infants between 35 and 36 weeks (gestational age) despite being of similar postnatal age. Furthermore, prolonged respiratory pauses and bursts of rapid breathing during nutritive sucking were more prominent in infants of a younger gestational age.

The neonatal suck: swallow: breathe (S:S:B) ratio also changes within the first 37 weeks post-conception (Bu'Lock et al., 1990). The optimal feeding ratio of these three behaviours is 1:1:1, which is not always achieved until 37 weeks post-conception (Bu'Lock et al., 1990). More detailed analysis of the S:S:B ratio revealed that preterm infants initially demonstrated coordinated suck: swallow (1:1) but only approximated coordinated swallowing and breathing as feeding efficiency improved (Lau et al., 2003). Thus, the authors speculated "feeding difficulties in preterm infants are more likely to result from inappropriate swallow-respiration interfacing than suck-swallow interaction" (Lau et al., 2003, p. 721).

In the first month of life, infants demonstrate an increase in swallowing efficiency, rate, and average duration of sucking (Qureshi, Vice, Taciak, Bosma, & Gewolb, 2002). Infant BSC also undergoes maturational change. This occurs even within the first five days of life: "with increasing age swallowing became more frequent; breathing became fully 'entrained' to the sucking rhythm and showed good co-ordination with swallowing" (Weber et al., 1986, p. 22).

Healthy newborns present with a variable pattern of coordination without an obvious preference for a particular respiratory phase during feeding (Bamford et al., 1992). Similarly, non-nutritive swallowing can occur during any phase of respiration (Daniels et al., 1990; Wilson et al., 1981). In human newborns 43% and 26% of nutritive swallows are followed by expiration and inspiration, respectively (Bamford et al., 1992). The variability in infant BSC may be further illustrated by the wide range of reported post-swallow expiration in nutritive swallowing: between 43% (Wilson et al., 1981) and 83% (Selley, Ellis et al., 1990). The BSC of adults, on the other hand, is much more predictable. Between 75-95% of swallows begin in the expiratory phase (Hiss et al., 2001; McFarland & Lund, 1995; Paydarfar et al., 1995; Preiksaitis et al., 1992; Shaker et al., 1992) compared to 39% in human newborns (Bamford et al., 1992). Similarly, 80-100% of water-induced and bolus swallows in adults are followed by expiration and only 1-4% by inspiration (Hiss et al., 2001; Klahn & Perlman, 1999; Preiksaitis et al., 1992; Shaker et al., 1992). These differences between adult and infant BSC indicate that considerable change must occur between the neonatal period and adulthood.

During nutritive swallowing, IE swallows are most common (up to 50% an individual neonate), followed by EE (up to 37% an individual neonate) (Bamford et al., 1992). These findings are in agreement with earlier research which indicates that nutritive swallows occur predominantly in the IE category, followed by EE, and occasionally in the EI categories (Selley, Ellis et al., 1990). This pattern changes within the first few weeks of life in preterm infants (Mizuno & Ueda, 2003). The proportion of IE, EE, and EI swallows all increased between 33 and 36 weeks post-conception (14.7% to 29.9%, 7.6% to 13.7%, and 10.5% to 18.6%, respectively). Term infants between the ages of five and eight days exhibit a more ‘mature’ coordination of breathing and swallowing than neonates around 2 days of age (Selley, Ellis, Flack, Curtis, & Callon, 1986). The older infants almost always swallowed in the IE respiratory-phase category (Selley et al., 1986). This highlights a maturational change within the first week of life. These authors, however, failed to replicate their findings in a later study in which no maturational changes in BSC were observed in very early infancy (Selley, Ellis et al., 1990). Unfortunately, statistical analyses to support their statements were not reported. Furthermore, Selley et al. (1990) obtained their data from a cross-section of twenty newborns between the ages of 8 hours and 6 days on a single occasion. Neither the precise age of each infant nor the mean age at the time of assessment was reported. Given this research design, it is likely that maturational processes were obfuscated and, thus, is not surprising that the results were not in agreement with those of Selley’s prior research.

The findings of Selley et al. (1986) are also only in partial agreement with a similar study conducted by Weber et al. (1986). Weber et al. also found that swallowing occurs during inspiration or expiration within the first 2 days of life. However, unlike the predominantly IE pattern of swallowing observed by Selley et al., some infants swallowed mainly in the EI category by five days of age. Unfortunately, statistical analyses were not performed nor were percentage values of each respiratory-phase category reported. The disagreement between these two studies may be a reflection of the instability of the infant system, or the result of the methodological approach employed by Weber et al. (1986). Similar to Selley et al. (1990), Weber et al. (1986) performed a once-off assessment on 12 infants between the ages of 2 and 6 days. This may not have been an adequate sample size for a cross-sectional study.

The proportion of swallows that occur during prolonged respiratory pauses also changes with age. Preterm and term infants swallow frequently during apnoeic periods (Bamford et al., 1992; Hanlon et al., 1997; Koenig et al., 1990; Lau et al., 2003; Mathew, 1988; Mizuno & Ueda, 2003). The percentage of nutritive swallows occurring during apnoeic periods decreases with maturation from 51% at 32-35 weeks post-conceptual age to 38% at term age, thereby approaching the 23% of term controls (Hanlon et al., 1997). Similarly, by adding those swallows associated with short respiratory pauses, it appears that nutritive swallows associated with respiratory pauses in preterm infants decreases from 58.7% to 38.9% between 33 and 36 weeks post-conception (Mizuno & Ueda, 2003). Preterm infants swallow more frequently during ‘apnoeic runs’ than during any other phase of respiration soon after the introduction of oral feeds (Lau et al., 2003). This pattern changed as the number of oral feeds increased such that apnoeic swallows were no greater than those preformed during inhalation (Lau et al., 2003).

Anatomical Maturation

The mature pattern of BSC characterized by predominantly post-swallow expiration is thought to be a protective mechanism against aspiration (McPherson et al., 1992). However, mammalian infants do not seem to demonstrate this pattern (Reix et al., 2003) and yet do not exhibit signs or symptoms of aspiration. Thus, either the mature pattern of BSC is not a protective mechanism, or infants must have alternative airway protection mechanisms. The absence of laryngeal vestibule penetration or aspiration during swallowing in mammalian infants may be the result of two anatomical features particular to infants. First, the relatively high position of the larynx is optimal for airway protection (Laitman & Reidenberg, 1993;

Negus, 1943). Second, the soft palate and epiglottis are thought to direct the bolus away from the laryngeal vestibule and into the oesophagus (Reix et al., 2003).

In the very young infant, the epiglottis-soft palate approximation (Figure 2.8) constructs a continuous passage between the nose and trachea (Sasaki, Levine, Laitman, & Crelin, 1977). This approximation is lost between 4 and 6 months of age, with intermittent and variable approximation only achieved during swallowing until 18 months of age (Sasaki et al., 1977). This would suggest a 'critical period' for the development of stable organisation of breathing during the transition from nasal to oral respiration (Sasaki et al., 1977). Anatomical changes such as elongation of the pharynx and the eruption of teeth are paralleled by neurological maturation (Walter, 1994).

During maturation the epiglottis-soft palate approximation and the high laryngeal position are lost as a result of the elongation of the pharynx and subsequent descent of the larynx and epiglottis (Figure 2.8). In humans, the epiglottis descends during infancy until an adult-like anatomical configuration may be achieved as late as adolescence (Schwartz & Keller, 1997). In adult humans, the hyolaryngeal complex displacement, which results from contraction of the suprahyoid muscles during swallowing, positions the larynx out of the path of the bolus (Logemann et al., 1992) and deflects the epiglottis (Lieberman, McCarthy, Hiiemae, & Palmer, 2001). Until recently, laryngeal descent during maturation was thought to be unique to humans as the foundation for development of speech. However, an MRI study has shown laryngeal descent in infant chimpanzees as well, suggesting that this maturational change is involved in swallowing and not only for speech in humans (Nishimura, Mikami, Suzuki, & Matsuzawa, 2003). Furthermore, the infant chimpanzee larynx descends rapidly and independently of the hyoid bone, which also likely reflects maturational changes of the swallowing mechanism (Nishimura et al., 2003). In human infants, the descent of the hyoid and larynx is most rapid between 9 and 33 months of age (Lieberman et al., 2001). The first of two major vertical and horizontal shifts of the supralaryngeal vocal tract occur before 1 year of age, and the second between 4.75 and 7.75 years, regardless of gender (Lieberman et al., 2001).

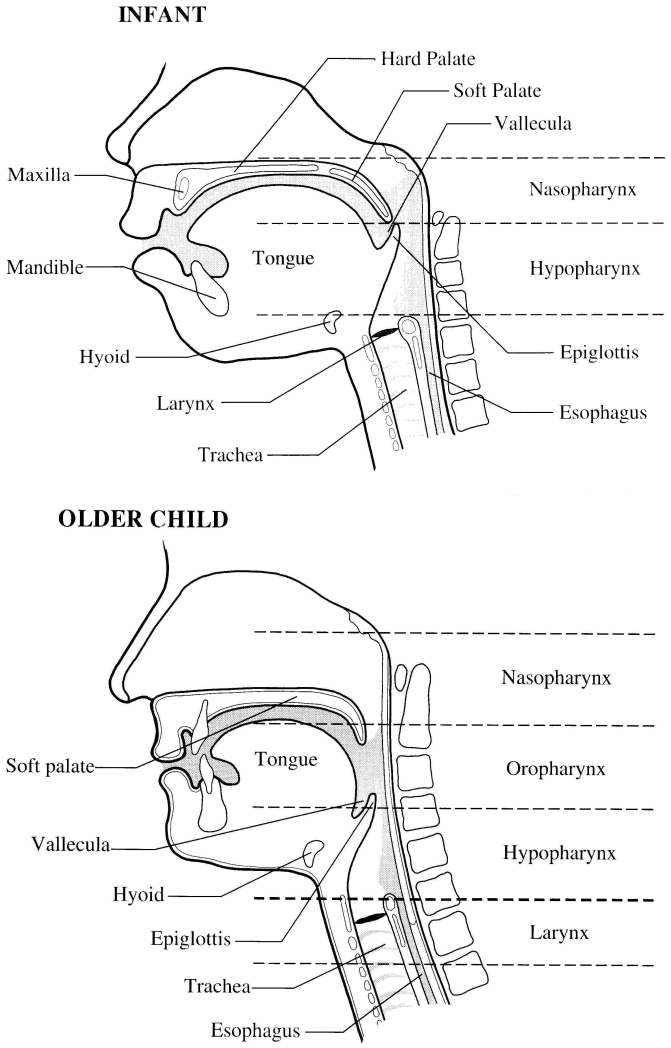


Figure 2.8 Breathing and swallowing anatomical structures of a human infant and older child. Note the loss of the epiglottic-soft palate approximation and elongation of the hypopharynx in the older child thereby approximating adult-like anatomy. From Arvedson, J. C., & Brodsky, L. (2002). Pediatric Swallowing and Feeding: Assessment and Management (2nd ed.). New York: Singular Publishing Group.

Neural Maturation

Although anatomical maturation in human infants may contribute to maturation of BSC, neural maturation must also contribute. The peripheral nervous system (PNS) undergoes postnatal maturation in animals (Lucier et al., 1979; Miller & Dunmire, 1976; Sumi, 1967), as do the respiratory- and swallowing-related neurones in the brainstem (Denavit-Saubie, Champagnat, & Fortin, 1997; Denavit-Saubie et al., 1994; Dutschmann, Morschel, Kron, & Herbert, 2004; Haddad & Getting, 1989; Rao, Jean, & Kessler, 1995, 1997; Schweitzer, Fortin, Beloeil, & Champagnat, 1992; Sumi, 1967; Takashima & Becker, 1986; Vincent & Tell, 1999). Miller (1999) argues that the maturation of the brainstem neural networks (central

pattern generators) may account for postnatal changes in mammalian infant BSC. Sumi (1967) hypothesized that, in cats, postnatal maturation of BSC is characterized by an increasing differentiation of brainstem controls for breathing and swallowing. Elicited oral reflexes diminish with increasing postnatal age in decerebrate animals where inhibitory encephalic input can be excluded (Thexton & Griffiths, 1979). This highlights the potential role of PNS and brainstem maturation in early BSC maturation. The restricted function of the cortex in the behaviour of infants is evident by the predominant display of brainstem-mediated reflexes (Chugani, 1998). Brainstem maturation may therefore account for a considerable component of the maturation of BSC in early infancy. The contribution of suprabulbar mechanisms to the maturation of BSC may come later in life.

There may be a 'critical period' during which suprabulbar structures become involved in infant feeding and BSC. Lesions to the lateral hypothalamus in the first day of life in rats resulted in longer latencies of nipple attachment and chronic low weight, but did not cause feeding problems once the rats were weaned (Almli, Hill, McMullen, & Fisher, 1979). The chronic low weight appeared to be associated only with the neonatal malnutrition and metabolic changes following the lesion. Interestingly, when the lateral hypothalamus of 7 and 14 day old rats were lesioned, suckling was impaired to the extent that without tube feeding the rats did not survive (Almli & Golden, 1974). Similarly, postweaned rats lesioned at 25 days and older demonstrated persisting feeding deficits and low body weight (review by Almli et al., 1979). These results suggest that there is a 'critical period' during which the neural mechanisms for feeding mature and before which dramatic reorganization of the immature rat lateral hypothalamus is possible (Almli & Fisher, 1985).

In agreement with the argument for protracted suprabulbar input into feeding, "oral feeding for the newborn is entirely reflexive. Rooting, nipple latching, sucking, and swallowing do not appear to require suprabulbar activity. Immediately after birth, however, the learning process begins with its dependence on experiential opportunities, sensory inputs, and suprabulbar neurologic maturation… in this way, feeding and swallowing gradually changes from a reflexive to a volitional process" (Stevenson & Allaire, 1991, p. 1449). Feeding is thought to become 'encephalized' with age so that "suprabulbar mechanisms become capable of utilizing the coordination resources of the medulla to accomplish qualitatively different performances" (Bosma, 1986, p. 214).

Although suprabulbar input may be minimal very early in life, as evident by the ability of anencephalic human infants to suck and swallow (Monnier & Willi, 1953), the descending undeveloped corticobulbar pathways in term newborns still serve important motor and sensory functions (Sarnat, 1989). Poor sucking, feeding, and swallowing coordination can result from cortical damage in neonates (Sarnat, 1989). Descending cortical input also augments brainstem and spinal cord reflexes, the former possibly including sucking and swallowing (Sarnat, 1989). “The reinforcement of suck and swallow reflexes by the corticobulbar tract remains speculative until confirmed by additional evidence, but the extensive clinical observations and neuropathy corroboration of the site of lesions suggest that this is the probable mechanism” (Sarnat, 1989, p. 159). With age, descending cortical input is thought to suppress feeding-related reflexes (Arvedson & Brodsky, 2002). The importance of descending regulatory input from the cortex is highlighted by the observation that oral movements similar to those observed in the rooting and sucking reflexes of newborns are observed in adult patients with diffuse cortical atrophy (Paulson & Gottlieb, 1968).

The mechanisms by which suprabulbar structures become more influential are through general maturation of the CNS. In general, postnatal maturation of the CNS of vertebrates involves the development of new synapses (Huttenlocher & Dabholkar, 1997), increases in the volume of grey and white matter (review by Sowell, Thompson, & Toga, 2004), and regressive activities such as the elimination of surplus synapses (Cowan, Fawcett, O'Leary, & Stanfield, 1984), and brain cell death (apoptosis) which reduces cell density (Rabinowicz, 1979). An MRI study demonstrated that brain maturation begins in the brainstem, followed by cerebellar and cerebral myelination (Barkovich, Kjos, Jackson, & Norman, 1988). Although the crucial period for the development of the cerebral cortex is between 24 and 32 weeks postconception (Gressens, Rogido, Paindaveine, & Sola, 2002), cortical development (review by Sowell et al., 2004) and myelination may continue into adulthood (Barkovich et al., 1988) and, thus, its input into swallowing and BSC may only be significant later in postnatal development.

The speed of the transmission of neural impulses between brain regions depends, in part, on the diameter of the axon and the thickness of the surrounding insulating myelin sheath (Aboitiz, Scheibel, Fisher, & Zaidel, 1992). Conduction velocity impacts on the speed of information processing (Swadlow, 1985). Although myelination of the CNS begins before birth (Ballesteros, Hansen, & Soila, 1993; Gibson, 1991) and continues into adulthood,

substantial changes occur within the first year (Van der Knaap & Valk, 1990) or 2 years (Kinney, Brody, Kloman, & Gilles, 1988), with the most rapid period of myelination occurring within the first 2 - 3 postnatal years (Ballesteros et al., 1993; Holland, Haas, Norman, Brant-Zawadzki, & Newton, 1986). There is a 74% increase in white matter volume (myelinated axons) between early childhood and adolescence (Courchesne et al., 2000). The bulbospinal pathways are myelinated at term, unlike the corticospinal and corticobulbar tracts, which only begin myelinating in the latter stages of gestation and becoming well myelinated by the age of 2 years (Sarnat, 1989). The duration of the myelination process of the corticopontine tract is the longest out of all the descending transcapsular tracts (Yakovlev & Lecours, 1967). Typically, sensory-related areas are myelinated before motor-related tracts and ultimately the association tracts (Barkovich et al., 1988). Although the corpus callosum contains some myelinated fibres soon after birth, the cerebellum is one of the first sites to become well myelinated, with the inferior peduncle fully myelinated by 3 months of age (Holland et al., 1986). Myelination of subcortical white matter is largely complete by 12 months (Holland et al., 1986). The cortex is unmyelinated at birth and follows a relatively protracted course of myelination (review by Gibson, 1991) but, by 2 years, infant and adult brains appear very similar (Ballesteros et al., 1993) with only gradual myelination of the cortex continuing into adolescence (Conel, 1939-1967 cited in Gibson, 1991). Gibson (1991) concluded that, given the degree of cortical myelination, the whole cortex is functional, at least on a basic level, between 1 and 2 years of age.

Unfortunately, many of the early studies on the developmental patterns of myelination were performed on infants who may not have been representative of the normal population (e.g., Barkovich et al., 1988; Holland et al., 1986; Kinney et al., 1988). For example, Kinney et al. (1988) found that the onset and rate of maturation of myelin appears to differ between sites within the brain, particularly between the lateral hemisphere of the cerebellum, the posterior limb of the cerebral cortex, the posterior frontal white matter and frontal pole. However, these data were obtained from infants, some of whom died as a result of SIDS, thus disputing the application of their findings to healthy infants.

SIDS is an unexpected death of sleeping infants (Reid, 2001), a death deemed unrelated to injury, accident, or organic disease (Byard & Krous, 2003). There may be a link between BSC and SIDS: possibly impaired cortical regulation (Sparks & Hunsaker, 2002) of respiration during sleep leads to the failure to resume respiration following SA and subsequent death (Jeffery et al., 1999). This is supported by the suggestion that immature neural control of BSC

may lead to life-threatening events in newborns (Praud & Reix, 2005). This argument is supported by two points that may be surmised from the literature and are described in detail below. First, impaired descending motor regulation can impair swallowing, and also lead to sudden infant death. Second, those centres involved in determining level of arousal influence BSC and, if faulty, may cause SIDS.

Future SIDS victims exhibit poor motor skills characterized by weak sucking, limited movement during sleep, and general hypotonia (Einspieler, Widder, Holzer, & Kenner, 1988). This is consistent with the hypomyelination seen in several CNS sites of autopsied SIDS victims, especially in pyramidal, cerebellar, and prefrontal-temporal-limbic pathways (Kinney et al., 1991). Although swallowing may not specifically engage all these pathways, the pyramidal tract, cerebellum, and frontal and temporal regions play a role in swallowing (Daniels & Foundas, 1997; Miller et al., 1997; Zald & Pardo, 1999). Patterns of hypomyelination in SIDS victims suggest that the central control of somatomotor and viscero-motor systems for cardio-respiratory control may be impaired and that SIDS may be the result of primarily a motor rather than a sensory disorder (Kinney et al., 1991). Sudden infant death typically occurs in infants between 1 and 6 months (Malloy & Freeman, 2004), an age group in which corticobulbar myelination should be developing substantially (Sarnat, 1989). The reason for the 1 – 6 months SIDS risk period is unclear, although some authors have purported that postnatal apoptosis in the medulla, cerebellum, and cerebrum, and the subsequent inadequate cardiorespiratory control results in SIDS (Sparks & Hunsaker, 2002).

Prior to death, SIDS victims have been found to have a higher incidence of apnoea during feeding and sleep than healthy infants of the same age (Steinschneider, Weinstein, & Diamond, 1982). Possibly the defensive activation of the hypothalamus and midbrain, which causes tachypnea in the presence of a noxious stimulus (Horn & Waldrop, 1998), is subdued by sleep in SIDS victims. In this instance, a build-up of secretions or reflux may be the noxious stimulus (Thach, 2000). Jeffery argues that “any impairment of swallowing or arousal or potentiation of the LCR response would augment this potentially lethal reflex response” (1999, p. 268). Sumi (1975) hypothesized that oropharyngeal stimulation and subsequent swallowing under certain circumstances, such as sleep and anaesthesia, may result in impaired organisational functioning of the immature medulla. Similarly, adult BSC is possibly altered by level of arousal (Kelly et al., in press) and anaesthesia (Nishino & Hiraga, 1991). Future SIDS victims are typically difficult to rouse from sleep (Einspieler et al., 1988) and always die during sleep (Reid, 2001). As discussed earlier, respiration, swallowing, and BSC may be

altered during sleep. The similarities between the features of SIDS and BSC suggest that similar neural mechanisms may be involved in both.

2.4.3.2 Breathing-Swallowing Coordination in Adults

Unlike infants, SA in adults typically occurs in mid-expiration (Clark, 1920; Hiss et al., 2001; Kelly et al., in press; Klahn & Perlman, 1999; Martin et al., 1994; Perlman et al., 2000; Preiksaitis et al., 1992; Preiksaitis & Mills, 1996; Smith et al., 1989). Despite this consensus, the precise frequency of SA occurring before, during, and after expiration differs greatly between studies. SA occurs during expiration (EE) between 62% (Hiss et al., 2001) and 94-100% (Martin et al., 1994). SA occurs before expiration (IE and EE) between 86% (Hiss et al., 2001) and 100% of the time (Klahn & Perlman, 1999), and after expiration (EI and EE) between 57% (Martin et al., 1994) and 93% (Klahn & Perlman, 1999) of the time.

The inconsistency in the literature may be the result of inconsistencies in three methodological features: statistical analysis, which makes the comparison of these studies difficult, data acquisition, and bolus administration. Evidence of the variety of statistical analyses is provided in Appendix B. The missing cells in the table in Appendix B reflect the differing methods of statistical analysis and reporting of data. For instance, some authors only reported the occurrence of post-swallow expiration (e.g., Selley et al., 1989a), others categorized swallows based on the preceding and/or following respiratory phases such as Preiksaitis and Mills (1996), or failed to provide a clear percentage breakdown of swallows within each respiratory-phase category (Smith et al., 1989). Moreover, some authors submitted grouped data obtained from different swallowing tasks for statistical analysis (Hiss et al., 2001), thus specific values for each task are unavailable.

As noted by other authors (Hiss et al., 2001; Klahn & Perlman, 1999), discrepancies in reported data may also be accounted for by the diverse range of respiratory equipment used by the different authors. The majority of BSC studies measured airflow direction at the nostril (Klahn & Perlman, 1999; Preiksaitis et al., 1992; Selley et al., 1989a, 1989b; Selley, Flack et al., 1990). Direction of nasal airflow is preferable to nasal thermistors when monitoring respiratory events (BaHammam, 2004). Nasal thermistors may respond to body temperature, thereby indicating a rise in temperature (indicative of expiration) in the absence of airflow (Tarrant, Ellis, Flack, & Selley, 1997). Respiratory plethysmography (Martin et al., 1994; Preiksaitis & Mills, 1996) is also problematic. Limb movements must be kept to a minimum

in order to minimize movement artifact (Tarrant et al., 1997). As a result, participants are spoon-fed the bolus, thereby creating a contrived feeding environment. Since swallowing involves the integration of sensory input (Miller, 1999), self-feeding may provide important sensory input. For this reason comparison between studies utilising self-feeding and researcher-controlled methods is difficult (Hiss et al., 2001). Some authors administered the boluses to the participants either via a syringe (Martin et al., 1994) or feeding utensil (Klahn & Perlman, 1999; Selley et al., 1989a; Smith et al., 1989), while others have allowed their participants to self-administer the boluses (Hiss et al., 2001; Kelly et al., in press; Preiksaitis & Mills, 1996).

Agreement amongst authors has been reached regarding the influence of discrete bolus volumes (ranging between 5 and 25 ml) which do not alter BSC (Hiss et al., 2001; Martin et al., 1994; Preiksaitis & Mills, 1996), regardless of bolus consistency (Preiksaitis & Mills, 1996). Sequential (serial/repetitive) drinking results in a higher incidence of post-swallow inspiration compared to the ingestion of discrete boluses (Hirst et al., 2002; Martin et al., 1994; Preiksaitis & Mills, 1996). This may be the result of the need for oxygen overruling the need to protect the airway. An increase in post-swallow inspiration was found for a sandwich meal compared to single-bolus swallowing (Preiksaitis & Mills, 1996), in contrast to the rarity of post-swallow inspiration during feeding reported by other studies (Hirst et al., 2002; Smith et al., 1989).

The impact of the introduction of a bolus on adult BSC is debatable given conflicting evidence in the literature. Some authors report no obvious difference in BSC between bolus and non-bolus swallows (Nishino et al., 1985), others report a trend towards increasing post-swallow expiration (Preiksaitis et al., 1992), or a significant increase in mid-expiratory swallows (Shaker et al., 1992) with the introduction of a bolus. The close association between swallowing and mid-expiration for nutritive swallowing in adults is supported by much research (Hiss et al., 2001; Kelly et al., in press; Klahn & Perlman, 1999; Martin et al., 1994; Perlman et al., 2000; Preiksaitis et al., 1992; Preiksaitis & Mills, 1996; Smith et al., 1989). Since the pattern of cortical excitation during volitional swallowing is greater than for reflexive swallowing (Kern, Jaradeh et al., 2001), it is possible that a greater cortical influence over BSC during voluntary swallowing is responsible for the close association of volitional swallowing and expiration.

BSC during volitional and reflexive swallowing has been compared (Kelly et al., in press; Nishino et al., 1985; Paydarfar et al., 1995; Shaker et al., 1992). However, as a result of the methodological approaches adopted, none of these studies excluded other variables that might account for difference between these two swallowing conditions. For instance, dry 'subconscious' swallows were performed during rest and not sleep (Shaker et al., 1992). Although volitional bolus ingestion resulted in an increase in mid-expiratory swallow proportions, the level of arousal and the degree of reflexivity in this condition is debatable given that the participants were awake and knew their BSC was being evaluated. As the supplementary motor cortex is active immediately prior to the execution of a volitional swallow (Huckabee et al., 2003), merely anticipating a swallow may activate the cortex. Moreover, the inclusion of the liquid bolus is sufficient to increase post-swallow expiration (Preiksaitis et al., 1992) and, thus, volition alone may not have been responsible for the increase in mid-expiration observed by Shaker et al.

It is possible that the inclusion of bolus swallows in both reflexive and volitional conditions (Paydarfar et al., 1995) would allow a more direct comparison between the two conditions. Paydarfar et al. compared self-syringed liquid swallows on cue to spontaneous liquid swallows. Spontaneous swallows were elicited in two ways: by slow infusion of water and by water injection at various points in the respiratory cycle through a flexible straw positioned in the oral cavity. It could be argued that the former 'reflexive' task is not truly representative of spontaneous 'subconscious' swallowing given the likelihood of anticipation and oral preparation on behalf of the participant. These authors focussed on the impact of swallowing condition on ensuing respiratory rhythms rather than the proportional distribution of swallows within the four standard respiratory-phase categories. Nonetheless, it seems that the reflexive bolus swallows frequently occurred at the inspiratory-expiratory cusp or in mid-expiration. This is unlike the predominantly mid-expiratory pattern reported by other authors for volitional bolus swallows (Hiss et al., 2001; Kelly et al., in press; Klahn & Perlman, 1999; Martin et al., 1994; Perlman et al., 2000; Preiksaitis et al., 1992; Shaker et al., 1992). This difference implies that neural control mechanisms for volitional and reflexive swallowing must impact upon BSC in healthy adults.

Nishino et al. (1985) took a slightly better approach albeit also problematic. They compared volitional dry swallows on command and water-induced reflexive swallows. Water-induced reflexive swallows occurred in all respiratory-phase categories, but predominantly in mid-expiration and without a difference between the two types of swallowing (Nishino et al.,

1985). Unfortunately, only those swallows preceded by specific breathing patterns were included, which may have biased the results. Water-induced swallows involved the introduction of 1 ml water boluses into the oropharyngeal cavity (through a mouthpiece). Although the water was introduced at random intervals, anticipation of the bolus may have allowed some degree of volitional control. Thus, it is doubtful that these swallows were truly reflexive. It would appear that the only condition in which truly non-volitional swallows can occur in neurologically intact humans is during sleep.

In a pilot study by Kelly et al. (in press), BSC during wake and sleep were compared. During sleep the proportion of EE swallows was lower and EI swallows higher than during wakefulness. However, like Nishino et al. (1985), a bolus was introduced in one condition (wakefulness) and not the other. Nonetheless, a condition interaction between age, gender, and condition was also found: elderly males exhibited higher proportions of EE swallows during wakefulness than sleep. Although Hiss et al. (2001) found that advancing age did not predict the pattern of EE swallows, other researchers have found an age effect on BSC. Elders initiate swallowing more frequently during inspiration than young adults (Shaker et al., 1992) and exhibit a high incidence of post-swallow inspiration (Hirst et al., 2002).

It is possible that changes in BSC with age are the result of neural changes associated with normal ageing. Recently it has been shown that there are changes in respiratory-related laryngeal coordination in healthy ageing rats, most likely a manifestation of poor sensorimotor integration (Nagai, Ota, Konopacki, & Connor, 2005). An increase in age results in neuronal shrinkage with a subsequent reduction in cortical volume (Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003) which is greater in the frontal and temporal lobes than the parietal lobe (review by Sowell et al., 2004). This is supported by evidence of neuronal loss in the cerebral cortex (Simic et al., 2005) and cerebellar cortex (Andersen, Gundersen, & Pakkenberg, 2003) with advancing age, most likely reflected in age-related changes in motor processing (Sailer, Dichgans, & Gerloff, 2000) and excitability (Peinemann, Lehner, Conrad, & Siebner, 2001). The latter effect on excitability may be a reflection of the diffuse thinning of white matter that comes with age (Resnick et al., 2003). Given the likely impact of sleep on sensory and motor function discussed earlier (section 2.4.2), possible decreased sensorimotor integration and limited cortical input in elders may account for the impact of sleep on BSC of elderly men (Kelly et al., in press).

2.5 Breathing-Swallowing Coordination: Some Unanswered Questions

There is still little known of the specifics of the neural substrates underlying BSC or SA in adults and, even more so, infants. This notwithstanding, it is clear that the brainstem plays a predominant role.

The impact of sleep on BSC and SA provides a useful indicator of the presence of suprabulbar influence, given the marked decrease in suprabulbar activity during sleep compared to wakefulness. The impact of volitional swallowing on BSC and SA compared to spontaneous wakeful swallowing has not yet been satisfactorily determined in adults, and since cortical input into volitional swallowing is more marked, comparison to spontaneous swallowing would further elucidate descending cortical influence in adults. This paradigm is somewhat more difficult to execute in the infant population from a behavioural perspective. The comparison of nutritive and non-nutritive wakeful swallowing most closely approximates the adult paradigm. This comparison has received no prior attention in healthy human infant, and would help elucidate the impact of sensory integration on BSC and SA.

There is limited data describing human foetal activities that potentially represent postnatal BSC or SA (Miller et al., 2003), and there is no data on the nature of the maturation of these behaviours in-utero or beyond 1 postnatal month in healthy term infants. It is clear from the literature that the pattern of infant BSC is somewhat different to that of adults; thus, postnatal maturation of the integration of breathing and swallowing in humans is implicit.

Methodical investigation of the biomechanics of infant BSC is also lacking. This is most likely due to the constraints on the investigative tools available to paediatric researchers. Given the vulnerability of the paediatric population, the use of important but invasive techniques such as videofluoroscopy (e.g., Ardran et al., 1958) and needle electromyography that may have been used many years ago are now prohibited. Ultrasound has been used in research that offered descriptive data on infant swallowing biomechanics (Bu'Lock et al., 1990) and may be a useful alternative to invasive techniques but is limited by the number of structures that can be visualized simultaneously.

The BSC and/or SA of adult patients with a wide range of abnormalities, including neurological (Pinnington, Muhiddin et al., 2000), respiratory (Shaker et al., 1992), and

structural (Hiss et al., 2003), have been compared to normal controls. However, very little data is available for infants, apart from preterm birth (Hanlon et al., 1997; Lau et al., 2003) and bronchiolitis (Pinnington, Smith et al., 2000). The only paediatric group with confirmed neurological damage that has been studied are older children with cerebral palsy (McPherson et al., 1992; Rempel & Moussavi, 2005). There appears no research on infants with structural damage such as cleft palate. Furthermore, the suspected important clinical link between aberrant patterns of BSC, such as a high incidence of post-swallow inspiration and aspiration in both adult and paediatric patient populations, is well-cited but has yet to be conclusively established. Also, as discussed above in section 2.4.3.1, the contribution of uncoordinated breathing and swallowing in SIDS remains unsolved.

Finally, there are no studies that document an effect of body position on infant BSC and very little on that of adults (McFarland et al., 1994; Shaker et al., 1992). There are well-established effects of body position on respiration and swallowing biomechanics and physiology, thus further investigation into the impact of body position on BSC is warranted. Body position may be an important variable to consider when designing future BSC research.

2.6 Hypotheses

The primary aim of the current research was to determine whether the cerebral cortex influences BSC and SAD. Infants were monitored longitudinally during their first year of life; a timeframe in which the cerebral cortex is known to develop substantially and potentially become increasingly involved in the mediation of swallowing.

Given the well-established marked reduction in cortical activation during NREM sleep, the sleep-wake paradigm was applied to both infants and adults. This was applied with the expectation that the impact of sleep on BSC and SAD in infants would increase with the development of the cortex to approximate adults.

In this thesis, studies representing infant data are presented in Part II and those for adults in Part III. The methodologies adopted for each participant group differ and are thus presented separately at the beginning of the relevant Parts. The chapters within each Part contain an abbreviated introduction leading to one or more hypotheses.

2.6.1 Hypotheses for Part II: Breathing-Swallowing Coordination in the First Year of Life

Hypothesis 1

Question: There is no known study that documents the longitudinal maturation of nutritive BSC in healthy infants beyond the first month of life (i.e., Lau et al., 2003).

Hypothesis: Infant nutritive BSC will change within the first year of life. This change will be characterized by an increase in the proportional distribution of swallows in the IE and EE respiratory-phase categories such that they will prevail over all other categories (II, EI, and P).

Justification: Nutritive BSC is expected to change within the first year of life given the reported changes within the first 5 days (Weber et al., 1986) or first month of life (Lau et al., 2003). The latter study provided greater detail on the nature of this early maturation and reported that the initially high proportion of swallows during 'apnoeic swallow runs' (during respiratory pauses of $\geq$ 2 s) decreased, and the proportion of swallows at the respiratory cusps (IE and EI) increased within the first month of life. However, the infant pattern described by Lau et al. is not the same as the IE- and EE-dominant pattern demonstrated by adults during serial swallowing (Issa & Porostocky, 1994) and, thus, maturation of BSC during breast- or bottle-feeding beyond 1 month of age is expected. Adult-like BSC is likely to be demonstrated once infants are anatomically and neurologically similar to adults. By the age of 1 year, epiglottic-soft palate approximation is lost (Lieberman et al., 2001) and substantial myelination of the CNS has occurred (Van der Knaap & Valk, 1990).

Significance: The potential impact of early sensorimotor feeding experience and the protracted impact of neural maturation (resulting in increasing descending cortical input), anatomical maturation, and respiratory system maturation on BSC will be elucidated. Furthermore, these normative data would provide a database for future comparison to the paediatric patient population with breathing and swallowing disorders, and potentially assist in the identification of pathologic patterns that interfere with feeding safety and efficiency.

Study design (Chapter 4): BSC during breast- or bottle-feeding was monitored longitudinally in ten healthy infants born at term. In anticipation of early maturation (Lau et al., 2003; Weber et al., 1986), BSC was monitored more frequently in the first 6 months than in the latter 6 months of the first year of life. Assessments were made within the first 48 hours, at 1, 2, 3, and 4 weeks, and at 2, 3, 6, 9, and 12 months of age.

Hypothesis 2

Question: The comparison between nutritive and non-nutritive BSC is not reported in the literature for human or animal neonates.

Hypothesis: Nutritive BSC will differ from non-nutritive wake BSC within the first 48 hours of life. This difference will be characterized by differing proportional distributions of swallows in at least two respiratory-phase categories, most likely one of which will be P swallow proportions. P swallow proportions will be greater during nutritive than non-nutritive swallowing.

Justification: The impact on infant BSC is likely to be substantial given two major features of neonatal physiology. First, feeding has a substantial effect on the cardiovascular system of healthy neonates (Cohen, Brown, & Myers, 1998). Second, sensory stimulation of the larynx evokes prolonged apnoea in infant animals (Lawson, Richter, Czyzyk-Krzeska, Bischoff, & Rudesill, 1991; Marchal, Corke, & Sundell, 1982; Storey & Johnson, 1975) and an exaggerated LCR with subsequent prolongation of apnoea in human infants (Thach, 1997). Thus, it is hypothesized that the sensory stimulation provided by feeding will result in an increase in swallows that occur during respiratory pauses or in succession (P respiratory-phase category).

Significance: The impact of oropharyngeal stimulation during breast- or bottle-feeding on BSC will provide insight into neonatal physiological response mechanisms, in particular the brainstem sensory integration.

Study design (Chapter 5): BSC during breast- or bottle-feeding was monitored and compared to BSC during non-nutritive swallows performed during wakefulness within the first 48 hours of life in ten healthy neonates born at term.

Hypothesis 3

Question: The comparison between nutritive and non-nutritive BSC is not reported in the literature for human or animal infants of any age.

Hypothesis: The difference between nutritive and non-nutritive BSC will change within the first year of life such that the impact of feeding is negligible by 1 year of age. At 1 year of age, the proportional distribution of swallows in all respiratory-phase categories will be similar for nutritive and non-nutritive conditions.

Justification: The neonatal response to oropharyngeal stimulation is likely to change with age as the PNS and CNS develop. This argument is supported by data obtained from animal research. The elicitation of pharyngeal swallowing results in complete cessation of respiration

in newborns (Harned et al., 1978; Lucier et al., 1979) but, at 2 - 3 months of age, the elicitation results in the alternation of respiration and swallowing (Harned et al., 1978). Furthermore, the impact of nutritive swallowing on adult BSC is negligible (Nishino et al., 1985), thus, it is anticipated that the impact of nutritive swallowing on BSC will decline and ultimately disappear with age to approximate an adult-like response.

Significance: The maturation of the impact of oropharyngeal stimulation during breast- or bottle-feeding on BSC will provide insight into the development of infant physiological response mechanisms. A maturing response would suggest that suprabulbar mechanisms become increasingly involved in the modulation of BSC.

Study design (Chapter 5): BSC during breast- or bottle-feeding was monitored and compared to BSC during non-nutritive swallows performed during wakefulness. These assessments were performed repeatedly in the first year of life to determine the point at which the impact of feeding on BSC matured.

Hypothesis 4

Question: Although Wilson et al. (1981) monitored infant non-nutritive BSC during sleep and wakefulness, no comparisons between the two conditions were made. Thus, the impact of sleep on neonatal BSC is unknown.

Hypothesis: Non-nutritive BSC during wakefulness will differ slightly from that during sleep in neonates within the first 48 hours of life. This difference will be characterized by a higher proportion of IE swallows and/or a lower proportion of EE swallows during sleep.

Justification: Prior research in adult humans (Kelly et al., in press; Nishino & Hiraga, 1991) and newborn animals (Reix et al., 2003) suggest that sleep or reduced level of arousal alters BSC as a result of the relative decrease in cortical control. Specifically, reduced level of arousal in adults either resulted in equal proportions of II and EE swallows (Nishino & Hiraga, 1991) or a higher proportion of IE swallows and a lower proportion of EE swallows (Kelly et al., in press). In newborn animals, there were lower proportions of IE and EI swallows during quiet sleep compared to wakefulness (Reix et al., 2003). The descending corticobulbar pathways in term newborns serve important motor and sensory functions (Sarnat, 1989) despite the neonatal cortex (Rabinowicz, 1979) and corticobulbar tracts being immature (Sarnat, 1989). Thus, neonatal suprabulbar input during wakefulness may be minimal and only slightly alter BSC.

Significance: The impact of sleep on BSC will provide an indication of whether the overall level of cortical activity during wakefulness is sufficient to alter newborn BSC. This would provide confirmation of cortical influence over BSC.

Study design (Chapter 6): BSC during non-nutritive swallowing conditions of sleep and wakefulness was monitored and compared in ten healthy neonates within the first 48 hours of life.

Hypothesis 5

Question: The impact of sleep on infant BSC during the first year of life is unknown.

Hypothesis: The impact of sleep on non-nutritive infant BSC will increase with age. The impact will be characterized by differing proportions of swallows in two or more of the following respiratory-phase categories: II, IE, EE, EI, and P swallows.

Justification: Given the likely impact of reduced level of arousal or sleep on the BSC of human adults (Kelly et al., in press; Nishino & Hiraga, 1991), it is expected that as the neural system of infants develops during infancy, the impact of sleep will become increasingly apparent during the first year of life. During postnatal development of the CNS, there is substantial synaptogenesis (Huttenlocher & Dabholkar, 1997), synaptic pruning (Sowell et al., 2004), increases in the volume of grey and white matter (review by Sowell et al., 2004), and myelination of the cortex (Gibson, 1991) and corticobulbar tracts (Sarnat, 1989), thus descending suprabulbar input, particularly during wakefulness, is likely to increase as a result.

Significance: An increase in the number of respiratory-phase categories subject to a condition effect, would suggest increasing descending cortical influence during wakefulness on BSC.

Study design (Chapter 6): BSC during non-nutritive swallowing conditions of sleep and wake was monitored in ten healthy neonates repeatedly within the first year of life to determine the point at which descending cortical influences (associated with increased level of arousal) alter BSC.

Hypothesis 6

Question: Direct comparison between neonatal or infant nutritive and non-nutritive SAD has not been previously reported.

Hypothesis: Throughout the first year of life, nutritive SAD will always be shorter than both non-nutritive wake and sleep SAD.

Justification: Evidence suggests that nutritive SAD of neonates may be substantially shorter than non-nutritive SAD, at 0.67 s (Hanlon et al., 1997) and 1.03 s (Wilson et al., 1981), respectively. Similarly, the introduction of a bolus may shorten SAD compared to non-nutritive swallows in adults (Miyazaki et al., 1994; Shaker et al., 1992), thus, it is anticipated

that SAD of nutritive swallows will be consistently shorter than non-nutritive swallows throughout the first year of life.

Significance: Persisting differences between nutritive and non-nutritive SAD throughout the first year of life, despite substantial suprabulbar maturation, will imply that the impact of feeding-related sensory input on SAD is an innate robust feature of human physiology and most likely brainstem-mediated. Absent maturation despite postnatal development of suprabulbar structures would imply that it is most likely brainstem-mediated.

Study design (Chapter 7): SAD of swallows performed during breast- or bottle-feeding and those performed during wakefulness and sleep was recorded in ten healthy infants repeatedly throughout the first year of life.

Hypothesis 7

Question: No prior research has investigated whether SAD during nutritive or non-nutritive swallowing matures in healthy term infants beyond the neonatal period. Hanlon et al. (1997) compared the SAD of term infants (under 1 week of age) and preterm infants. Although these authors provided longitudinal data on preterm infants, the term infants were not assessed beyond the first week of age.

Hypothesis: The SAD of nutritive swallows, wake non-nutritive swallows, and sleep non-nutritive swallows will not change with age.

Justification: The SAD of all three types of swallowing will not change with age, given the similarities in SAD between infants and adults. The combined mean SAD of preterm and term infants is 530 ms (Koenig et al., 1990) which is similar to adult SAD of 550 ms (Issa, 1994) for nutritive swallows. Non-nutritive infant SAD is 1.03 s (Wilson et al., 1981) which is also is similar to the reported mean non-nutritive SAD in adults ranging from 860 ms to 1410 ms (Hiss et al., 2001).

Significance: The absence of maturation of nutritive and non-nutritive SAD throughout the first year of life will imply that SAD is an innate robust feature of human physiology, and therefore most likely brainstem-mediated.

Study design (Chapter 7): SAD of swallows performed during breast- or bottle-feeding and those performed during wakefulness and sleep was recorded in ten healthy infants repeatedly throughout the first year of life.

2.6.2 Hypotheses for Part III: Breathing-Swallowing Coordination in Adulthood

Hypothesis 8

Question: McFarland et al. (1994) compared BSC in the upright position to resting on the hands and knees (quadruped position) and found that SA shifted from early to late expiration in the upright position. On the other hand, Shaker et al. (1992) found no change in BSC between vertical and horizontal positions. This apparent conflict could reflect the differences in the adopted horizontal positions: quadruped (McFarland et al., 1994) and supine (Shaker et al., 1992). There appears to be no research comparing the effect of horizontal body positions on BSC (e.g., prone vs. supine vs. side-lying). Thus, further research is required to determine whether BSC differs between these horizontal positions and between horizontal and vertical (upright) positions.

Hypothesis: Adult non-nutritive BSC during volitional swallowing will differ between horizontal (supine, side-lying, and prone) and vertical (upright) positions.

Justification: There is evidence that certain features of respiration such as lung capacity, compliance, and maximal expiratory pressure, are altered by a shift between vertical and horizontal positions (Badr et al., 2002; Behrakis et al., 1983; Manning et al., 1999). A change in body position from vertical to horizontal may also alter pharyngeal transit times (Ingervall & Lantz, 1973), upper oesophageal sphincter (Castell et al., 1990; Johnsson et al., 1995), and distal esophageal functioning (Chang et al., 1996). The vertical-horizontal effect on respiration and swallowing suggests that BSC may, too, be altered by a shift in position on the vertical-horizontal plane.

Significance: If BSC is altered by body position, this would imply that BSC is sensitive to position-related peripheral neural feedback rather than being a purely predetermined and invariant brainstem-generated pattern. Alternatively, altered BSC may reflect a shift of SA within the respiratory-phase cycle as a result of altered breathing and/or swallowing biomechanics. This may also have implications for future research methods. Body position may be an important variable to consider in the design of BSC studies.

Study design (Chapter 9): The BSC during volitional swallows performed by twenty healthy adults was monitored in four body positions: three in horizontal plane (supine, side-lying, and prone) and one in vertical plane (sitting upright).

Hypothesis 9

Question: Prior research suggests that level of arousal influences BSC in human adults (Kelly et al., in press; Nishino & Hiraga, 1991). However, due to methodological flaws in these studies (discussed in detail in section 2.4.2.2) the effect of reduced level of arousal in healthy individuals remains inconclusive.

Hypothesis: Adult non-nutritive BSC will differ between non-volitional swallowing conditions that vary in terms of the level of arousal, such as non-volitional swallows performed during wakefulness and those performed during NREM sleep. Specifically, the proportion of IE swallows will increase and the proportion of EE swallows will decrease with decreasing level of arousal.

Justification: Although the pilot study was problematic (Kelly et al., in press), it suggested that the proportion of IE swallows increases and the proportion of EE swallows decreases during sleep. In this hypothesis, NREM sleep was specifically chosen to represent a non-volitional condition under which cortical activation is substantially reduced compared to wakefulness. The global cerebral blood flow and energy metabolism during NREM sleep is less than REM sleep (Madsen et al., 1991) and wakefulness (Braun et al., 1997; Maquet, 2000). Thus, swallows performed during NREM sleep could be considered the diametrical opposite of cortically-regulated swallows.

Significance: The influence of increased level of arousal, together with the influence of increased level of volition (Hypothesis 10), will help elucidate the extent of the role of cortical centres in the control of BSC.

Study design (Chapter 10): Whilst controlling for body position, the BSC of twenty healthy adults was monitored under the following non-nutritive swallowing conditions: non-volitional wake and non-volitional NREM sleep.

Hypothesis 10

Question: Prior research demonstrated BSC during natural sleep differs to that of wakefulness (Kelly et al., in press). However, voluntary liquid swallows were included in the wake but not the sleep condition. Thus, the condition effect observed may be due to either increased swallowing volitional control or the sensory input provided by the liquid bolus. Thus, the effect of level of volitional control over swallowing on BSC remains unclear.

Hypothesis: Adult non-nutritive BSC will differ between swallowing conditions that vary in the degree of volitional input. Specifically, the proportion of IE swallows will increase and

the proportion of EE swallows will decrease as the level of volitional control over wakeful swallowing decreases.

Justification: Although the pilot study was problematic (Kelly et al., in press), it suggests that the proportion of IE swallows decreases and the proportion of EE swallows increases with increasing volitional control. fMRI studies suggest that the degree of cortical activity is greater for volitional than non-volitional swallows (Kern, Jaradeh et al., 2001; Martin et al., 2001). Thus, altered BSC during volitional swallowing would suggest that those cortical sites involved in volitional swallowing may also modulate BSC.

Significance: The influence of increased volitional control will elucidate whether an increase in cortical control over swallowing plays a substantial role in organizing swallowing-respiratory behaviours. This has implications for patients with cortical damage who may have diminished volitional control over swallowing and therefore exhibit aberrant patterns of BSC.

Study design (Chapter 10): Whilst controlling for body position, the BSC of twenty healthy adults was monitored during the execution of non-nutritive volitional and non-volitional wake swallows.

Hypothesis 11

Question: Although prior research has reported on the effect of arousal from sleep on the frequency of swallowing (Kahrilas et al., 1987; Lear, 1965; Lichter & Muir, 1975), none have specifically addressed the impact of arousal from sleep on BSC.

Hypothesis: Adult non-nutritive BSC will differ between NREM sleep swallows that are immediately followed by arousal from sleep and those that are not.

Justification: Arousal is associated with an increase in the level of cortical activity and increased efferent and afferent system excitability (review by Akerstedt et al., 2002) as well as altered swallowing (Castiglione et al., 1993; Kahrilas et al., 1987; Lear, 1965; Lichter & Muir, 1975) and respiratory behaviour (Jordan, Eckert, Catcheside, & McEvoy, 2003). During NREM sleep, the phasic activities of pharyngeal and diaphragmatic muscles of healthy humans are altered following momentary electrocortical arousal (Carlson et al., 1994). Given the above effects on swallowing and respiratory phenomena, arousal from sleep may influence BSC.

Significance: Arousal-associated change in BSC would provide further support for cortical influence over BSC since arousal from sleep entails cortical activation (review by Akerstedt et al., 2002).

Study design (Chapter 11): The BSC of twenty healthy adults was monitored during overnight sleep such that non-nutritive swallows preceded by NREM sleep and followed immediately by arousal could be recorded.

2.6.3 Hypotheses for Part IV: Breathing-Swallowing Coordination Across the Lifespan

Hypothesis 12

Question: The maturation of non-nutritive BSC in humans across the lifespan is unknown as there are no previous published data.

Hypothesis: Non-nutritive BSC of non-volitional wake swallows will differ between infants (neonates and one-year-olds) and adults (young and elderly). Specifically, infants are expected to exhibit lower proportions of IE and EE swallows.

Justification: Prior research suggests that human infant non-nutritive swallowing may not be adult-like. Non-nutritive infant swallows (wake and sleep) can occur in any respiratory-phase category (Wilson et al., 1981). Although the exact proportional distribution of swallows in each respiratory-phase category is unclear, this seemingly variable pattern appears different from the close association of non-nutritive non-volitional swallows with respiratory-phase categories involving post-swallow expiration in young adults (Shaker et al., 1992). Thus, it is expected that infants will exhibit lower proportions of swallows in those categories that are associated with post-swallow expiration (IE and EE).

Significance: Maturation of BSC between infancy and adulthood, and subsequent increase in the incidence post-swallow expiration (IE and EE) as a protective mechanism against aspiration (McPherson et al., 1992), may reflect neural maturation. Since suprabulbar influences may mediate BSC in adults (Kelly et al., in press) the maturation of BSC may reflect increasing descending suprabulbar input. This is possible given that CNS myelination continues beyond the first year of life (Ballesteros et al., 1993; Conel, 1939-1967 cited in Gibson, 1991; Courchesne et al., 2000; Holland et al., 1986; Kinney et al., 1988; Sarnat, 1989). There are also changes in CNS, including the brainstem and cortex, that are associated with the normal ageing process (Alvarez et al., 2000; Andersen et al., 2003; Ransmayr et al., 2000; Resnick et al., 2003; Simic et al., 2005; review by Sowell et al., 2004; Tang, Lopez, & Baloh, 2001-2002) and which may be sufficient to alter the BSC of elderly individuals.

Study design (Chapter 12): The BSC of spontaneous swallows of ten infants, ten young adults, and ten elderly adults was monitored whilst lying awake in supine and being distracted by external activities.

PART II: BREATHING-SWALLOWING COORDINATION IN THE FIRST YEAR OF LIFE

Chapter 3. Methods: Infants

3.1 Participants

Ten healthy term neonates (eight females, two males) were recruited by advertisement (Appendix C) following approval from the Canterbury Regional Health Ethics Committee. Written consent was obtained from a parent of each neonate (Appendix D). The neonates were born to mothers without prenatal maternal complications, were born at or above 38 weeks gestational age, and presented with Apgar scores[4] at or above '7' at 5 min after birth (Francis, Self, & Horwitz, 1987). The neonates had no reported medical complications at birth, nor did they have nervous system or upper-body structural abnormalities.

3.2 Participant Tasks

BSC of newborn infants was monitored under three conditions which differed in terms of the degree of volitional control over swallowing and the degree of overall cortical activity. At one end of this continuum were nutritive swallows performed during feeding. At the other end of the continuum were reflexive saliva swallows performed during sleep. Between these two conditions, were spontaneous (naïve) saliva swallows performed during caregiver/investigator interaction. The infant and caregiver governed the order in which these conditions were conducted although attempts were made to follow the following sequence:

Condition A - Spontaneous saliva swallows were performed while the infant was awake, lying in supine position and interacting with the caregiver or investigator.

Condition B - Nutritive swallows were performed during feeding at liberty from either the breast or bottle, as determined by the caregiver, in a reclined position. Attempts were made to only include breast feeding swallows and to ensure the use of the same feeding modality for consecutive assessments to eliminate a potential modality effect. However, bottle-feeding could not be avoided in three infants as a result of maternal health concerns such as milk production problems or maternal anaemia.

[4] APGAR scores are calculated according to the neonate's appearance (skin colouration), pulse (heart rate), grimace (responsiveness or "reflex irritability"), activity (muscle tone), and respiration (breathing rate and effort). A score of '7' and above is considered normal.

Condition C - Spontaneous sleep swallows of saliva were performed during day-time sleep in supine position.

Assessment under these three conditions were made within the first 48 hours after birth, at 1, 2, 3, and 4 weeks, and at 2, 3, 6, 9, and 12 months of age. The number of swallows performed in each condition was determined by the infants' cooperation, duration of sleep, and, to a lesser extent, parental time constraints. Sleep was subjectively monitored by the investigator and caregiver and confirmed by failure of the infant to respond to auditory stimuli. Recording was momentarily halted if mouth-breathing was suspected based on observation. Attempts to keep a supine body position consistent across conditions and assessment ages were made given the known physiological effects of altered body position in infants (Chen et al., 1995) and so that swallows performed in each condition were comparable. However, due to behavioural constraints this was not always possible particularly during wakefulness and sleep at 9 months and 1 year of age.

3.3 Materials

Simultaneous time-locked recordings of submental muscle activity, thyroid acoustics, and the direction of nasal airflow determined the coordination of breathing and swallowing for all participants. A mercury switch position monitor recorded the body position of infants over the age of 9 months. These measurements were all captured by an integrated hardware-software system (Kay Elemetrics Swallowing Workstation) to allow for the analysis of temporal relationships between measures.

3.3.1 Submental Surface Electromyography

Submental surface electromyography (SEMG) measured the muscle activity associated with the contraction the submental muscles and reflects a relative measure of hyolaryngeal excursion (Sonies, Gottlieb, Solomon, Matthews, & Huckabee, 1996). The collective submental muscle group consists of the mylohyoid, geniohyoid, and anterior digastric muscles (Ertekin & Aydogdu, 2003). Submental SEMG was used to detect swallows in infants. Wilson (1981) found that electrodes placed over the chin and hyoid bone, with an ear electrode as a reference point, was a reliable method. Although the use of a pharyngeal catheter to detect swallowing-related pharyngeal muscle contraction would increase the identification of swallows (Wilson et al., 1981), pharyngeal catheters were not used due to

their likely impact on swallow stimulation and BSC and the increased level of undesirable invasiveness. The skin was cleaned using alcohol and Cor-gel electrolyte gel was applied to 2 cm silver chloride SEMG electrodes (Thought Technology Triode^{TM}). The collective submental muscle group was located by palpation and the two active bipolar SEMG electrodes were positioned over this muscle group. Due to limited submental space between the mandibular process and hyoid, the active electrodes were positioned at a right angle to the mylohyoid muscles and the reference electrode was positioned on the forehead. The submental SEMG signal was amplified, then bandpass filtered (50-220 Hz), rectified, lowpass filtered at 3 Hz, and digitized at 250 Hz.

3.3.2 Laryngeal Microphone

Thyroid acoustics were used to rule out submental SEMG artifact and confirm swallowing onset in infants (Hanlon et al., 1997; Pinnington, Smith et al., 2000). Thyroid acoustics were measured by a laryngeal microphone (Figure 3.1) positioned lateral to the thyroid (Takahashi, Groher, & Michi, 1994) which was located by palpation and held or taped in position with standard surgical tape. The microphone was a modified omnidirectional condenser microphone with a sensitivity of -62 ± 3 dB, an impedance of < 2.0 kΩ, and a frequency response of 50-12,500 Hz. The microphone was connected to a preamplifier (Rolls mini-mic preamplifier MP13, gain of 6-50 dB, Figure 3.2). The signal from the preamplifier was sampled at 4000 Hz. The signal from the preamplifier was collected at 250 Hz by the swallowing workstation via the acoustic channel.

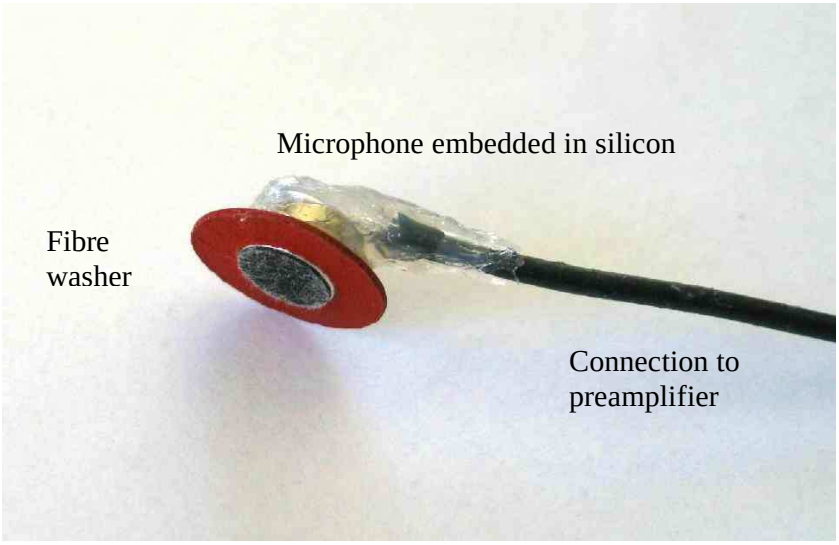


Figure 3.1 The laryngeal microphone consisting of an omnidirectional condenser microphone embedded in silicon and a fibre washer.

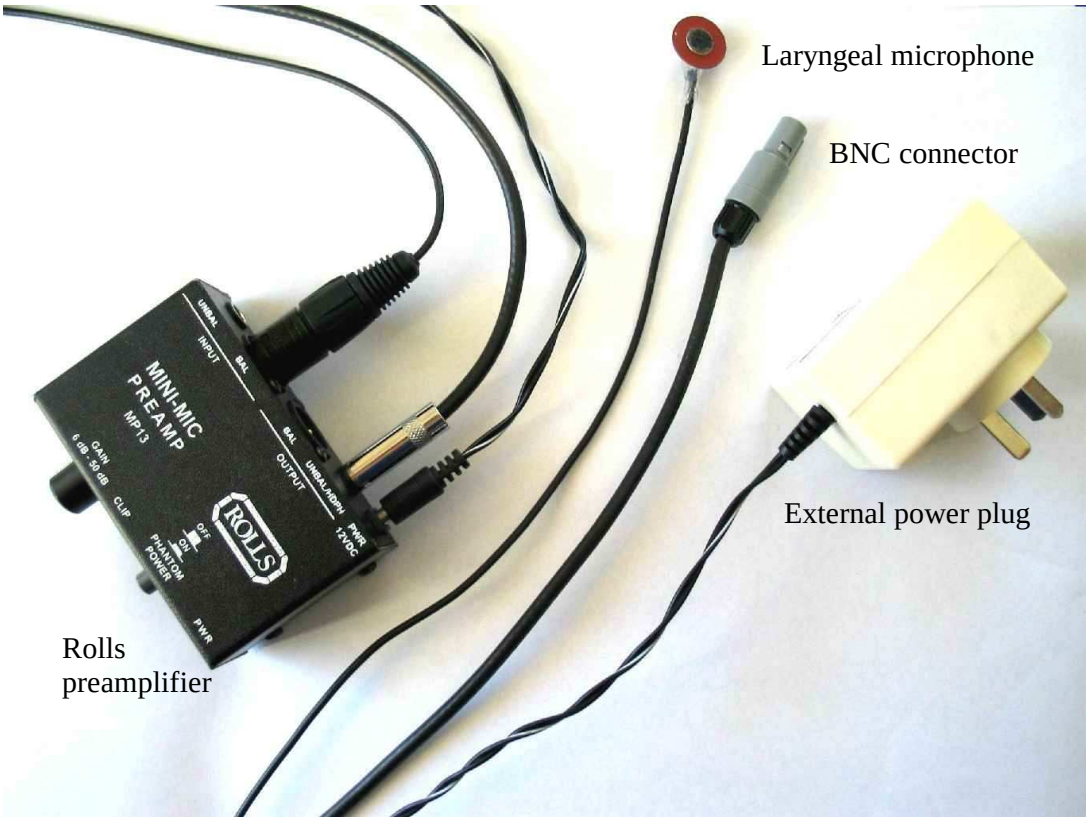


Figure 3.2 The laryngeal microphone and Rolls mini-mic preamplifier (MP13).

3.3.3 Nasal Cannula

Nasal airflow, using a nasal cannula of an appropriate size, was recorded in order to determine the respiratory phase cycle preceding and following each swallow in infants (Hanlon et al., 1997; Thach & Menon, 1985) and to determine the duration of SA. Nasal prongs were situated at the entrance to each nostril and secured firmly around the head and the other end attached to the nasal channel of the swallowing workstation. The signal was sampled at 250 Hz.

3.3.4 Mercury Switch Position Monitor

Body position was monitored using custom-made mercury switch position monitor secured to a soft elasticized band fitted around the chest with Velcro© at the level of the xiphisternum from 9 months of age (Figure 3.3). A change in body position resulted in a change in the output voltage which correlated to one of four body positions: side-lying (left = 1.02 V, right = 0.69 V), upright (1.55 V), supine (0.35 V) and prone (1.33 V). The mercury switch position monitor was connected to a custom-made sensor box, which also acted as an external battery-

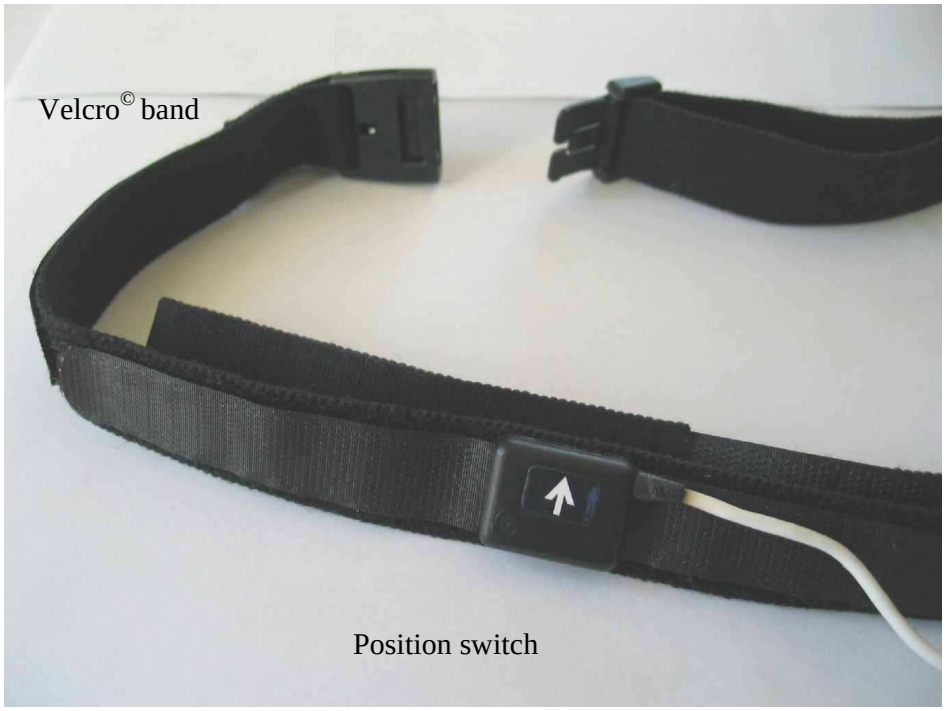


Figure 3.3 The mercury switch position monitor fitted to an elasticized Velcro© band.

operated power source, and the output fed into the auxiliary channel of the swallowing workstation. The signal was sampled at 250 Hz.

3.4 Procedure

The infants and their caregivers were made comfortable in the birthing facility (Burwood Hospital, Christchurch) or the University of Canterbury Swallowing Rehabilitation Research Laboratory following which the SEMG electrodes, nasal cannula, and laryngeal microphone were fitted. BSC was monitored during wakefulness, during feeding from either the breast or bottle in a reclined position and then during sleep for as long as the infant tolerated the procedure, fed or slept, respectively. Caregivers were instructed to feed their infants either in the standard breast feeding position (lying on their backs facing their parent) or in positions similar to that of breast feeding (cradled in their arms or in supine). Sleep, characterized by closed eyes in the presence or absence of regular breathing and small body movements (Prechtl, 1974), was subjectively monitored by the investigator and caregiver and confirmed by failure of the infant to respond to auditory stimuli. The duration of each assessment lasted approximately 5 hours and occasionally infants had to return the following day if all conditions could not be assessed. The number of swallows attained in each session was

governed by three phenomena: the infants' cooperation, duration of sleep and to a lesser extent parental time constraints.

Measures of normal development recorded by a developmental nurse (i.e., weight and head circumference) were documented at each assessment. As a rudimentary assessment of neurological development, reflexes that were appropriate for their chronological age were assessed by the investigator until they no longer persisted. These reflexes were the walking, grasp, rooting, moro, babinski, and tonic neck reflex (Appendix E). From 1 month of age the Denver Developmental Screening Test II (Frankenburg, Dodds, Archer, Shapiro, & Bresnick, 1992) was also completed by the author to monitor the achievement of normal developmental milestones.

The entire procedure was carried out on all ten infants within the first 48 hours, at 1, 2, 3, and 4 weeks, and at 2, 3, 6, 9, and 12 months of age[5]. The original aim was to assess infants within the first *and* second 24 hours of life; however, due to limited access to newborns within the first 2 days and behavioural issues, such as minimal waking time, this was not possible for all infants. Thus, the 'first 48-hour' data included data obtained during either the first or second 24 hours, or where possible, data obtained during both the first *and* second 24 hours. In the latter event, BSC and SAD data for a particular condition were averaged to represent the entire 48-hour period for the relevant infant. Behavioural constraints, such as poor infant compliance, made data collection difficult from 9 months of age. It was therefore decided to terminate the data collection at 1 year instead of the originally proposed 18 months.

3.5 Data Analysis

Swallows were identified by simultaneous bursts of SEMG activity and thyroid acoustics paired with a cessation in nasal airflow. All swallows were assigned to one of five categories based on the phase of respiration preceding and following the SA: inspiration-SA-inspiration (II), inspiration-SA-expiration (IE), expiration-SA-expiration (EE), expiration-SA-inspiration (EI), and mid-pause (P). An example of an infant nutritive swallow is shown in Figure 3.4. Inspiration and expiration was identified by negative and positive pressure amplitudes, respectively. Mid-pause swallows were those that occurred during prolonged apnoeic pauses

[5] These assessment ages were strictly controlled for where possible (taking into account parental constraints and transient infant illnesses), particularly within the first month of life.

(Figure 3.5) and included two or more consecutive swallows, between which no respiration occurred, also known as ‘apnoeic swallow runs’ (Lau et al., 2003). The duration of benign apnoeic pauses in healthy infants may be as little as 2 s (Curzi-Dascalova & Christova-Gueorguieva, 1983; Hoppenbrouwers et al., 1980) or as long as 15 s (Hoppenbrouwers et al., 1977) and may co-occur with swallowing (Don & Waters, 2003; Menon et al., 1984; Miller & DiFiore, 1995). Since benign pauses are, in part, characterized by absent nasal airflow, the SA of swallows that occur during an apnoeic pause cannot be identified and were therefore excluded from duration analyses. During a swallow, the absence of nasal airflow, represented by a black flat line on abscissa of the respiratory recording on the computer screen, was taken to indicate SA (Figure 3.6). SAD was measured manually using the computer cursor to determine the precise duration of the shaded apnoeic area. This was performed on all swallows except for P swallows since swallowing-specific apnoea cannot be determined when imbedded in a prolonged respiratory pause. Furthermore, the effect of BSC on SAD is not addressed in this thesis since swallowing did not necessarily occur in all of the four remaining respiratory-phase categories (II, IE, EE, and EI) in all conditions for all individuals. Thus, a single mean SAD value for each condition was calculated for each individual based on the means of those respiratory-phase categories that were represented.

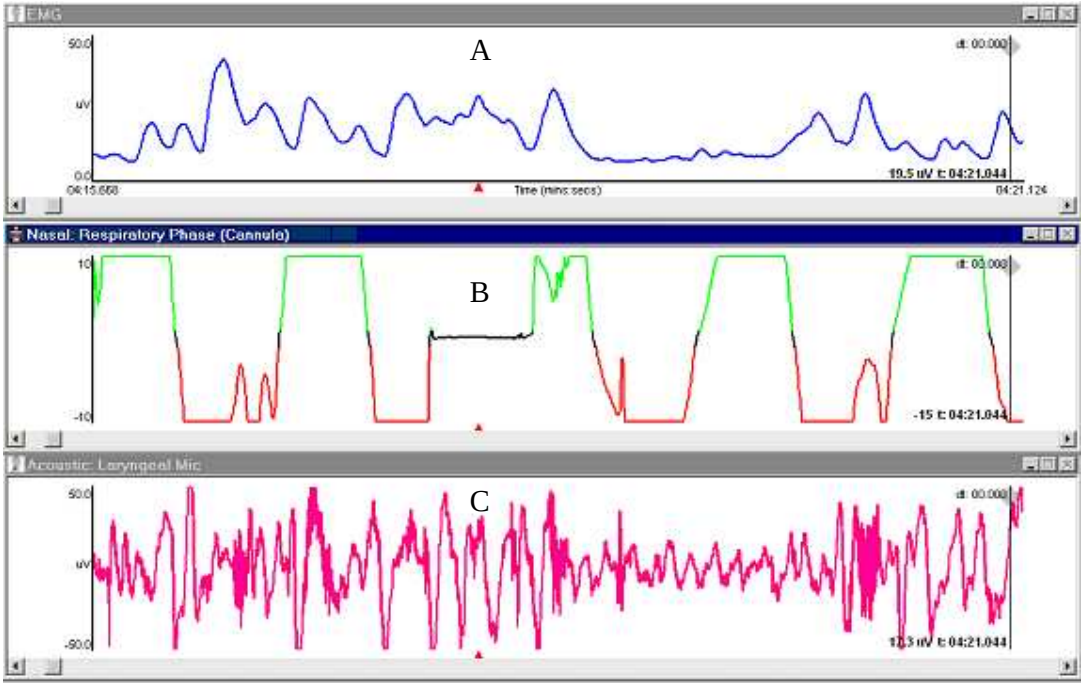


Figure 3.4 An IE swallow of a healthy six-month-old female during breast feeding during approximately 6 s of recording. The swallow is identified by a burst of submental surface electromyography activity (A), paired with a cessation of respiration (swallowing apnoea) (B) and a burst of acoustic activity (C). The swallow is classified according to the respiratory phase preceding and following swallowing apnoea (positive = expiration, negative = inspiration).

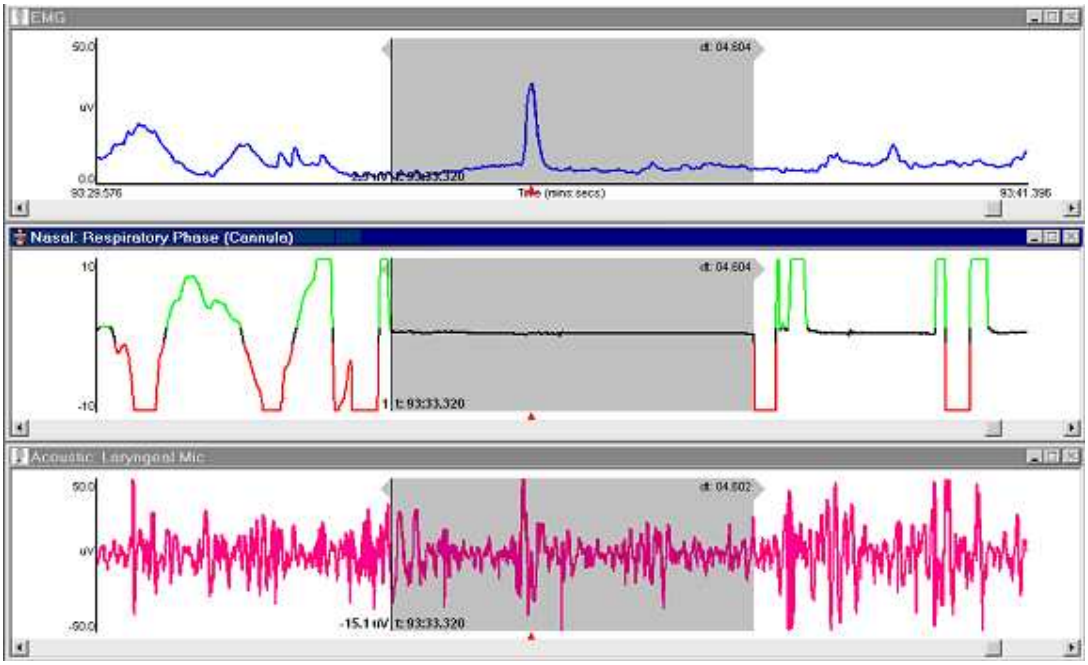


Figure 3.5 A sleep swallow of a healthy one-week-old female during a 4.5 s respiratory pause (shaded area) during approximately 11 s of recording (i.e., a 'P' swallow).

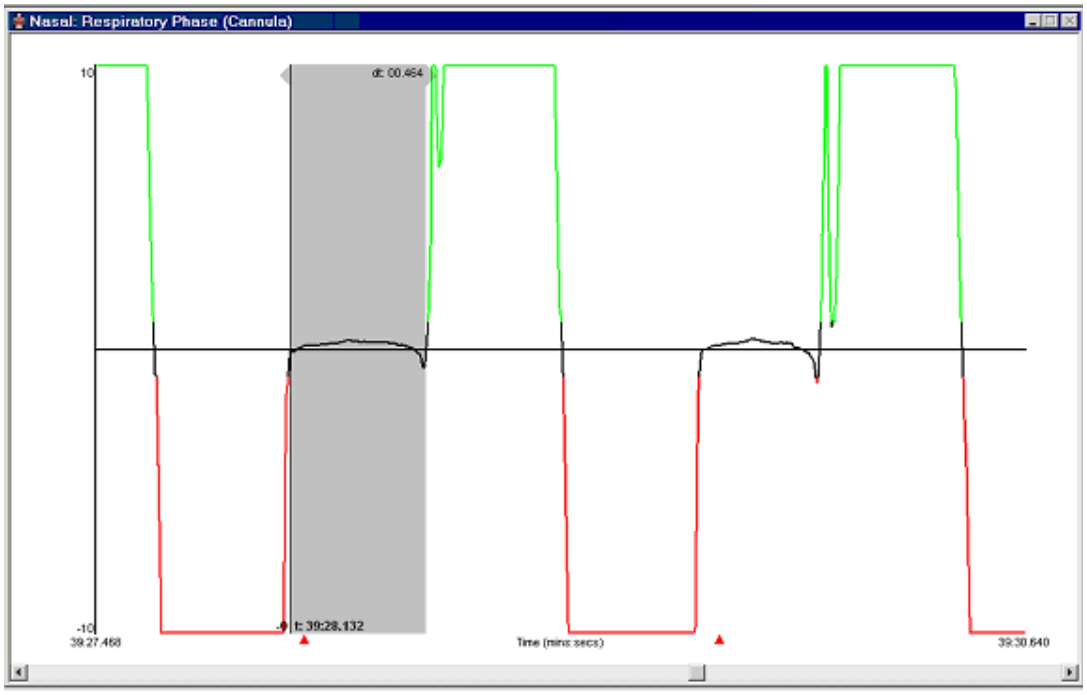


Figure 3.6 Measuring the duration of swallowing apnoea (shaded area = 464 ms) of a mid-expiratory (EE) sleep swallow of a healthy 48-hour-old female, during approximately 3 s of recording.

3.6 Data Processing, Preparation, and Statistical Analyses

Further details concerning data processing, preparation, and statistical analyses are described in the following chapters. All infant statistics were performed using the Statistical Package for the Social Sciences (SPSS, version 11.5, 2002, or version 13.0, 2004) and a p-value < 0.05 was taken to indicate statistical significance.

Chapter 4. Maturation of Nutritive Breathing-Swallowing Coordination in the First Year of Life

4.1 Introduction

Healthy human newborns reportedly present with a variable pattern of coordination without an obvious preferred respiratory phase (Bamford et al., 1992). Other data obtained from healthy term infants have been tainted by the inclusion of data obtained from preterm infants (Hanlon et al., 1997; Koenig et al., 1990) or from infants differing in postnatal age within the first week of life (Selley, Ellis et al., 1990). The need for tight control of postnatal age is highlighted by the observation that BSC changes within the first 5 days (Weber et al., 1986).

There is minimal information on the maturation of BSC in the healthy human infant population. Although studies have addressed the maturation in preterm infants (Lau et al., 2003; Mizuno & Ueda, 2003), none have clearly documented that of healthy term infants beyond 1 month of age (Lau et al., 2003). The majority of research on the BSC of healthy term infants (Bamford et al., 1992; Koenig et al., 1990; Selley, Ellis et al., 1990; Selley et al., 1986; Weber et al., 1986) has involved single assessments and, hence, longitudinal data are lacking. Two of the longitudinal studies (Selley et al., 1986; Weber et al., 1986) reported maturational changes when comparing newborns and infants that were a few days older, but these reports were merely descriptions of observations rather than detailed methodical investigations with subsequent statistical analyses.

Lau et al. (2003) appear to be the only researchers to have completed a longitudinal assessment of healthy term infants. They found that the BSC of term infants within the first week of life was different to the pattern generated between 2 and 4 weeks of age. This maturation was primarily characterized by a decrease in the number of swallows that occurred during ‘apnoeic swallow runs’ (during respiratory pauses of ≥ 2 s). The pattern of BSC in the term infants changed within the first month of life; swallows at the respiratory cusps (between expiration and inspiration) increased in frequency to approximately 57% of the total number of swallows. Although the proportional distribution of swallows were not reported, Issa and Porostocky (1994) described two BSC patterns associated with serial swallowing in adults that may be equated to IE and EE respiratory-phase categories. Martin et al. (1994) found that

the preferred BSC pattern varied between adult individuals during serial swallowing; most participants performed multiple swallows prior to expiration, however some individuals resumed respiration with inspiration. Overall proportional distributions of swallows were also not reported by Martin et al. Nonetheless, the difference between neonatal and adult BSC during serial swallowing suggests that the maturation process is incomplete by 1 month of age and thus further longitudinal investigation is warranted.

Normative data from older infants are crucial for the identification of deviant patterns and may play an important role in clinical decision-making given the importance of adequate respiratory-swallow integration in adult (Morton et al., 2002; Nilsson et al., 1997) and paediatric patient populations (McPherson et al., 1992; Miller & Kiatchoosakun, 2004; Pinnington, Smith et al., 2000). Research has identified atypical BSC during feeding in children with cerebral palsy (McPherson et al., 1992) and bronchiolitis (Pinnington, Smith et al., 2000), in whom swallowing and feeding are often compromised (McPherson et al., 1992; Pinnington, Smith et al., 2000). Increases in post-swallow inspiration compared to healthy controls have been identified in both groups (McPherson et al., 1992; Pinnington, Smith et al., 2000), as well as in adult patients with specific neurological damage (Hadjikoutis et al., 2000). Thus, post-swallow inspiration may be indicative of disordered respiration and/or swallowing (Hadjikoutis et al., 2000) and of patients at particular risk of aspiration (McPherson et al., 1992).

A precursor to understanding the potential link between respiratory and swallowing integration during feeding in the paediatric patient population is to establish the nature of typical integration patterns in the healthy human infant population. Given that there are strong links between adequate cardiorespiratory control and efficient feeding (Daniels et al., 1986; Daniels et al., 1988; Daniels et al., 1990; Pinnington, Smith et al., 2000), further investigation of the integrative processes is crucial. Furthermore, a longitudinal study provides information that is fundamental to the understanding of human growth and development of respiratory-swallowing integration. Therefore, in this chapter, longitudinal BSC data obtained from healthy term infants between 2 days and 1 year of age during breast- or bottle-feeding are presented.

4.2 Hypothesis 1

Infant nutritive BSC will change within the first year of life. This change will be characterized by an increase in the proportional distribution of swallows in the IE and EE respiratory-phase categories such that they will prevail over all other categories (II, EI, and P).

4.3 Data Processing and Preparation

Feeding swallows were identified by simultaneous bursts of SEMG activity and thyroid acoustics paired with a cessation in nasal airflow and classified by the primary raters (BK and LR) as II, IE, EE, EI, or P. A random 18 assessments (approximately 17% of all feeding swallows) were reanalysed by the primary raters and independent raters (LL, BK, and LH) in order to determine intraclass correlation coefficients for intra- and inter-rater reliability, respectively. Repeated-measures ANOVA were used to analyse the effects of age and feeding method on the relative frequencies of the different respiratory-phase categories. Respiratory-phase category and age were entered as within-subject effects and method of feeding as a between-subject factor for each age-group analysis. The sphericity assumption for repeated-measures was tested using Mauchly's test (Mauchly, 1940) and when this assumption was not met the Greenhouse-Geisser correction was applied to the significance tests. Where significant main or interaction effects were found ($p < 0.05$), they were further explored using Fisher's protected least significant difference (LSD) tests.

4.4 Results

A total of 15,073 feeding swallows were analysed. There were over 100 swallows in each respiratory-phase category for all assessment ages with the exception of mid-pause swallows in which the three older age groups had less than 50 swallows (Figure 4.1). Intraclass correlation coefficients demonstrated strong inter- and intra-rater reliability for respiratory-phase categorization ($r = .989$ and $r = .964$, respectively).

The proportion of swallows followed by expiration at each age are as follows: 48 hours (69.4%), 1 week (59.9%) 2 weeks (57.3%), 3 weeks (69.3%), 4 weeks (58.1%), 2 months (53.7%), 3 months (60.3%), 6 months (75.0%), 9 months (72.6%), and 12 months (74.4%). A repeated-measures ANOVA was performed to compare respiratory-phase categorization data

across all assessment ages to determine the effects of age on BSC. This analysis revealed no main age effect [$F(2.21, 19.9) = 2.40$, $p = .112$] but a respiratory-phase category effect [$F(4, 36) = 35.0$, $p < 0.001$]. Fisher's LSD test revealed differences between the following respiratory-phase categories: IE (M = 35.0%, SE ± 2.5%) and II (M = 12.9%, SE ± 1.7%), IE and P (M = 6.2%, SE ± 1.1%), and P and EE (M = 30.0%, SE ± 1.5%). EI did not differ from any other respiratory-phase category (M = 15.9%, SE ± 2.1%). Approximately 65% of all swallows were followed by expiration (sum of IE and EE).

There was also an interaction between age and respiratory-phase category [$F(5.83, 52.4) = 2.71$, $p = 0.024$]. Further exploration of this interaction using Fisher's LSD indicated that the significant respiratory-phase category effects depicted above were largely consistent across ages but also indicated age-related changes in the differences between IE and EI, II and EE, EI and EE, EI and P, once between II and P, but never between II and EI. Of particular interest were the differences between IE and EE at 48 hours and 1 year, with EE being dominant in the former age group and IE being dominant in the latter age group. At 48 hours, infants swallowed more frequently during EE but by 1 week IE swallows had become, and continued to be, the most common category (Figure 4.2). In order to further assess changes over time within each respiratory-phase category, separate repeated-measures ANOVAs were conducted for each respiratory-phase category. No age effects were found for II [$F(9, 81) = 1.69$, $p = .105$] and EI [$F(9, 81) = 1.03$, $p = 0.426$], however, there were age effects for IE [$F(9, 81) = 3.85$, $p < 0.001$], EE [$F(9, 81) = 2.58$, $p = 0.012$], and P [$F(9, 81) = 3.93$, $p < 0.001$] categories. The LSD test was applied to data on consecutive ages to explore the nature of these age effects. This revealed an increase in IE swallows between the ages 9 months and 1 year. A decrease was noted for EE swallows between 48 hours and 1 week. There were no differences between consecutive ages for P swallows and, hence, the age effect is due to the gradual decrease in P swallows.

In order to determine the effect of feeding method on BSC, repeated-measures ANOVAs were performed for each assessment age where the method of feeding was not homogeneous. Only within the first 48 hours of life were all ten infants breast-fed. These analyses revealed no association between the method of feeding and the relative frequency of the respiratory-phase categories over all ages or within each age group. Although the sample size is small for both breast-fed and bottle-fed infant groups, the means and standard deviations of the percentage frequency occurrence of swallows are similar for both groups (Table 4.1).

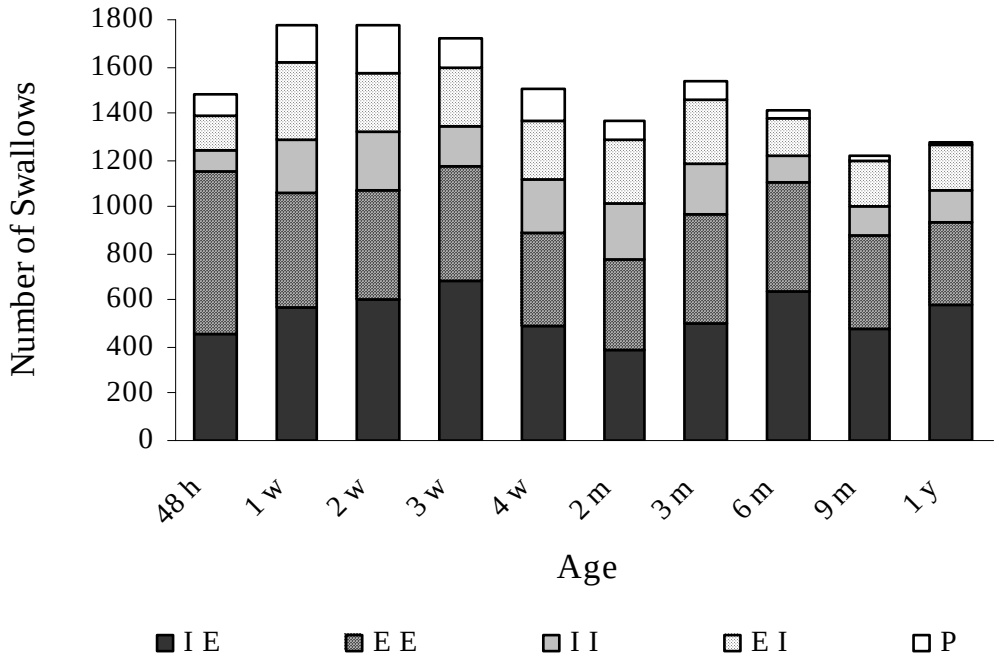


Figure 4.1 The raw number of swallows in each of the five respiratory-phase categories at each assessment age.
Note: II = inspiration-SA-inspiration, IE = inspiration-SA-expiration, EE = expiration-SA-expiration, EI = expiration-SA-inspiration, P = mid-pause, h = hours, w = week, m = months, y = year

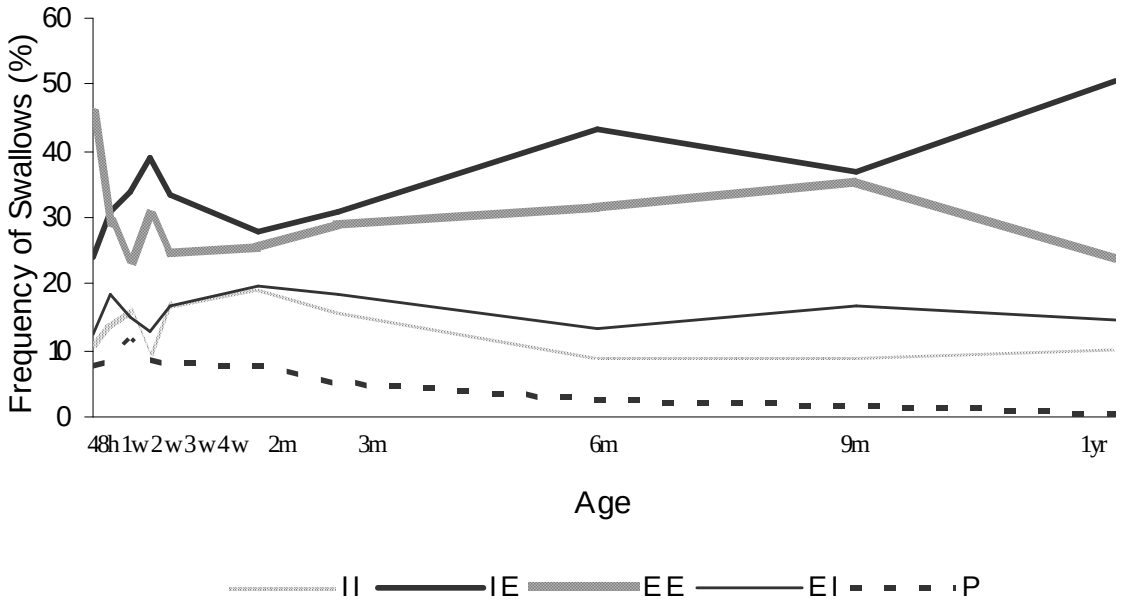


Figure 4.2 Proportional distribution of swallows in each respiratory-phase category over time.
Note: The data represented in this graph are not continuous data, but rather data obtained at discrete ages, displayed in this manner for ease of reference, II = inspiration-SA-inspiration, IE = inspiration-SA-expiration, EE = expiration-SA-expiration, EI = expiration-SA-inspiration, P = mid-pause, h = hours, w = week, m = months, y = year

Table 4.1 Proportional Distribution of Swallows in Each Respiratory-Phase Category for Breast and Bottle-fed Infants, Irrespective of Age

	Feeding Modality			
	Breast Frequency (%)		Bottle Frequency (%)	
Respiratory-phase Category	M	SD	M	SD
II	13.8	10.7	9.8	7.4
IE	35.7	17.0	37.8	10.7
EE	27.4	12.2	31.4	12.2
EI	16.1	10.6	16.4	7.8
P	6.9	7.0	4.6	7.2

Note: II = inspiration-SA-inspiration, IE = inspiration-SA-expiration, EE = expiration-SA-expiration, EI = expiration-SA-inspiration, P = mid-pause, M = mean, SD = standard deviation

4.5 Discussion

This is the first longitudinal study to document the maturation of BSC during feeding of healthy term infants within the first year of life. Over 15,000 swallows were recorded, substantially more than earlier studies (e.g., 462 swallows in preterm infants, Wilson et al, 1981). Infants in the present study exhibited adult-like characteristics. First, continuous swallows in adults typically occur in mid-expiration or between inspiration and expiration, with the majority of swallows preceding expiration (Issa & Porostocky, 1994). Second, the majority of nutritive swallows (65%) were followed by expiration irrespective of age. By 6 months, 75% of swallows were followed by expiration. Previous research in adults indicates between approximately 63.5% and 100% thin liquid swallows are followed by expiration (Hirst et al., 2002; Hiss et al., 2001; Klahn & Perlman, 1999; Martin et al., 1994; Preiksaitis et al., 1992; Preiksaitis & Mills, 1996). Thus, these particular features of infant BSC are similar to those of adults.

Substantial maturation patterns were seen in the mid-pause and end-expiratory phase categories. Within the first 2 days of life, there was a higher proportion of swallows in mid-

expiration (EE) than during any other respiratory-phase category. By 1 week, however, the proportion of EE swallows decreased to a level similar to IE swallows. Very little change in the pattern of BSC was observed between 1 week and 3 months of age. However, from 6 months the large majority of swallows were followed by expiration (> 72%). At 12 months there was a dramatic increase in IE swallows proportions; such that they dominated EE swallows. The trend towards IE dominance over EE, which is achieved by 12 months perhaps indicates a growing preference to expire after a swallow when lung volume is as it's greatest (Lau et al., 2003). Throughout the year there was a gradual decrease in the proportion of P swallows which is similar to the decline in swallowing during respiratory pauses in preterms with age (Hanlon et al., 1997; Mizuno & Ueda, 2003). The association of prolonged respiratory pauses with non-nutritive swallowing in infants could be either peripherally or centrally instigated (Praud & Reix, 2005). Peripheral stimulation of pharyngeal and laryngeal sensory receptors may induce apnoea and swallowing (Praud & Reix, 2005). Alternatively, central respiratory-swallowing neural interaction in the brainstem during apnoea may trigger swallowing (Praud & Reix, 2005). Both hypotheses could apply to nutritive swallowing. However, the declining P swallows in the present study may merely be a reflection of the decline in the frequency of respiratory pauses in the maturing respiratory system (Carse, Wilkinson, Whyte, Henderson-Smart, & Johnson, 1981; Hoppenbrouwers et al., 1977; Poets, Steebens, Alexander, & Southall, 1991). Nonetheless, the overall pattern of maturation was largely governed by two shifts: the first occurring within the first week of life, followed by a plateau and the second between 3 and 12 months during which further modifications were seen. The early maturation process may have been the result of postnatal sensory-motor experience and the latter the impact of relatively protracted neural and anatomical maturation.

The effect of early postnatal feeding experience in the present study is similar to that of prior research that indicates infants between the ages of 5 and 8 days exhibit more 'mature' BSC, most often in IE, than their 2-day old counterparts who swallow less frequently in the IE category (Selley et al., 1986). However, the results of the present study are not in agreement with those of Bamford et al. (1992) who found that, within the first 48 hours of life, IE swallows occurred more often than EE swallows (23.5% vs. 14%, respectively) in contrast to the present findings of 24.0% vs. 45.4%, respectively. A possible explanation for this discrepancy is the way in which swallows were categorized. Bamford et al. (1992) created a further five categories from those swallows occurring during apnoeic pauses (inspiration-pause, expiration-pause, pause-pause, pause-inspiration, pause-expiration) and defined a pause as a cessation in respiration of greater than 150 ms. Although this categorization has

been used again more recently (Mizuno & Ueda, 2003; Mizuno, Ueda, & Takeuchi, 2002), the justification for this classification system based on 150 ms is unclear and may have led to the inclusion of more swallows in the P category and fewer in the remaining four expiratory and inspiratory categories.

The change observed within the first week of life highlights the potential impact of early postnatal experience on the CPGs that coordinate breathing and swallowing. Stevenson and Allaire summarize this process: “oral feeding for the newborn is entirely reflexive. Rooting, nipple latching, sucking, and swallowing do not appear to require suprabulbar activity. Immediately after birth, however, the learning process begins with its dependence on experiential opportunities, sensory inputs, and suprabulbar neurologic maturation… in this way, feeding and swallowing gradually changes from a reflexive to a volitional process” (1991, p. 1449). This statement is echoed by the likely impact of early experiences on the cytoarchitecture of the cortex (Chugani, 1998). In the present study, the increase of IE swallows with age may be the result of PNS and CNS maturation associated with postnatal sensory-motor experience. The PNS matures dramatically in the first 2 years of human life (Parano, Uncini, Devivo, & Lovelace, 1993). Postnatal maturation of the brainstem and peripheral nerves appears responsible for the maturation of feeding-related reflexes in animals (Thexton & Griffiths, 1979). Thus, it is possible that this maturation accounted, at least in part, for the changes observed in the first year of life of the infants in the present study.

Suprabulbar input is also a likely contributor to the maturation of BSC, given evidence that it contributes to similar functions such as feeding behaviour and oral reflexes. First, the development of new synapses in the human cortex continues throughout the first 2 years of life (Huttenlocher & Dabholkar, 1997). Second, documentation exists of a ‘critical period’ in which the lateral hypothalamus becomes important in the feeding behaviour of infant rats (Almli et al., 1979). Third, it has been suggested that descending cortical input may augment brainstem reflexes such as sucking and swallowing and suppress stereotypical reflexes (Sarnat, 1989). This is supported by clinical observations that feeding and swallowing disorders can result from cortical damage in human neonates (Sarnat, 1989). By 2 - 3 months, cortical metabolism of glucose is higher than in the neonatal period, although specific frontal lobe metabolism only increases at 6 - 12 months (Chugani, 1998). Similarly, the cerebral cortex of infants increases in thickness between birth and 6 months (Rabinowicz, 1979). These patterns roughly coincide with the time at which the large majority of swallows are followed by expiration, and more specifically, the tendency for IE swallow proportions to

increase in the present study, suggesting a possible link. Furthermore, oral movements similar to those observed in the rooting and sucking reflexes of newborns have been observed in adult patients with diffuse cortical atrophy thereby indicating the importance of descending regulatory input from the cortex (Paulson & Gottlieb, 1968). Postnatal myelination, which is important for neural transmission (Aboitiz et al., 1992), may result in increased descending input from suprabulbar neural structures. Myelination of the neural connections between the cortex and the brainstem (the corticobulbar tract) occurs primarily during the first 2 years of human life (Sarnat, 1989) during which descending suprabulbar input is likely to increase. In general, the patterns of myelination coincide with developmental feeding milestones in the first year of life such as postnatal myelination of important swallow-related sites and the emergence of voluntary feeding behaviours (review by Rogers & Arvedson, 2005).

Another likely contributor to the maturation of BSC in the first year of life is anatomical change, specifically the descent of the hyoid bone and larynx during which the epiglottis-to-soft-palate approximation is lost between 4 and 6 months of age (Sasaki et al., 1977). This approximation allows a continuous passage between the nose and trachea (Laitman & Reidenberg, 1997). This age coincides with the age at which the large majority of swallows are followed by expiration during feeding observed at 6 months in the present study. By 6 months, nine of the ten infants were tolerating solid food in-take. Infants typically tolerate a variety of food textures by 6 months of age as a result of the maturation of the digestive system and tongue action (Rogers & Arvedson, 2005). This coincides with the disappearance of certain feeding-related reflexes by 6 months (e.g., the rooting reflex) as a result of descending cortical inhibition (Arvedson & Brodsky, 2002). In the healthy infant, both neural and anatomical maturation influence respiration and swallowing, thus the impact on the coordination of breathing and swallowing is inevitable. With this in mind, the present study provides important developmental data that will allow for future comparison to infants with anatomical anomalies of the head and neck (e.g., cleft palate), neurological impairment, and respiratory and swallowing disorders.

The present study indicates that early postnatal feeding experience, paired with the relative protracted neural and anatomical maturation, and not environmental factors (i.e., method of feeding or type of ingested fluid), account for the observed changes in the pattern of BSC in the first year of life. Previous research suggests that environmental factors influence infant feeding biomechanics. Tongue biomechanics of breast-fed infants differs to that of bottle-fed infants (Weber et al., 1986) and, according to Qureshi et al., “suck or swallow rate, pressure

generated, or volume intake may differ in breast- and bottle-fed infants, the underlying rhythmicity and patterning of suck and swallow rhythms are less likely to be influenced by feeding modality" (2002, p. 39). Comparison of breast-fed and bottle-fed infants in the present study revealed no differences in the patterns of BSC between these two groups. This is supported by the similarity in the means and standard deviations between the two groups. Thus, the absence of an effect of method of feeding on the relative frequency of the respiratory-phase categories in the ANOVA likely reflects a true finding rather than a manifestation of the small sample size.

4.6 Conclusions

For the first time, the maturational patterns of the integration of breathing and swallowing during feeding in healthy term infants beyond 1 month of life are described. Irrespective of age, the majority of feeding swallows are followed by expiration even soon after birth, a pattern reported in the literature for nutritive swallows in adults. Although this pattern is adult-like from birth, further breakdown of these post-swallow expiratory swallows into IE and EE categories, reveals maturation patterns particularly evident within the first week of life (EE dominant), followed by increasing IE swallow proportions until, by 1 year, infant BSC is IE dominant. Dominance of EE and IE swallows appear to be the preferred respiratory-phase categories of adult serial swallowing (Issa & Porostocky, 1994), suggesting infant BSC may be fully mature by 1 year. The early maturation of BSC may have been the result of postnatal sensory-motor experience. The later maturation of this coordination may have been the result of the relatively protracted impact of neural, anatomical and respiratory system maturation. These data provide a detailed longitudinal description of normative processes. Future comparisons to infants with breathing and swallowing disorders may thus identify pathologic patterns that interfere with feeding safety and efficiency.

Chapter 5. Effect of Feeding on Infant Breathing-Swallowing Coordination

5.1 Introduction

BSC during feeding matures in early infancy in both term and preterm infants (Lau et al., 2003; Mizuno & Ueda, 2003). The previous chapter indicates that the maturation of nutritive BSC continues late into infancy. In terms of non-nutritive BSC in animals, infant (Reix, Arsenault, Langlois, Niyonsenga, & Praud, 2004; Reix et al., 2003) and adult patterns (Feroah, Forster, Fuentes, Lang et al., 2002) are very similar, suggesting that non-nutritive BSC is adult-like at birth (Reix et al., 2004). However, there are no published data on whether this is true for humans (Praud & Reix, 2005), nor comparisons of nutritive and non-nutritive swallowing conditions in human infants.

It is likely that feeding has an impact on BSC given reports of the dramatic effect on the cardiovascular system of healthy neonates (Cohen et al., 1998) and the effect of sensory input on other aspects of infant feeding such as suck motor patterns (Finan & Barlow, 1998), sucking rate (Burke, 1977), and the ratio of sucks to swallows (Burke, 1977). There is also a close association of apnoea and bradycardia with post-swallow pharyngeal residue (Itani, Fujioka, Nishimura, Niitsu, & Oono, 1988) which highlights the impact of pharyngeal stimulation on the respiration of premature infants. Laryngeal sensory stimulation in infant animals typically evokes prolonged apnoea (Lawson et al., 1991; Marchal et al., 1982; Storey & Johnson, 1975). The response to sensory stimulation of the LCR may be particularly exaggerated during sleep in premature ovines (Marchal et al., 1982). Oropharyngeal stimulation provided by gastroesophageal reflux may stimulate an exaggerated LCR with subsequent prolongation of apnoea (Thach, 1997) and may even contribute to sudden infant death (Thach, 2000). Similarly, Steinschneider et al. (1982, p. 858) stated there is a “general hypothesis that prolonged apnoea or airway obstruction is part of the pathophysiologic process resulting in SIDS…” and that “…unstable respiratory activity during sleep as well as apnoea and pharyngeal/laryngeal dysfunction induced by liquid stimulation of the upper airway” are implicated. Further to this, immature neural control of BSC may lead to life-threatening events in newborns (Praud & Reix, 2005), thus the impact of pharyngeal stimulation on the BSC of infants warrants further investigation.

The neural networks that organize swallowing, respiration, mastication (Miller, 1999), and sucking (Finan & Barlow, 1998) are found in the brainstem and are influenced by sensory feedback (Miller, 1999). This is supported by evidence that the activity of brainstem respiratory neurones and respiration are altered during laryngeal stimulation in piglets (Lawson et al., 1991). Although the precise mechanisms governing BSC and the maturation thereof in human infants are unclear, evidence from decerebrate animals suggests that the brainstem is heavily involved (Wallois, Khater-Boidin, Dusaussoy, & Duron, 1993). Since cranial nerves involved in respiration and swallowing (Marlot & Duron, 1979) and suprabulbar structures (Gibson, 1991) mature postnatally in mammals, these structures may also play a role in the maturation of BSC in human infants. Maturation of the nervous system is likely to result in reduced response to sensory simulation. This is supported by animal research that documents a more dramatic effect of oral electrical stimulation on breathing and swallowing in the young than in the adult animal (Wallois et al., 1993). Furthermore, the elicitation of swallowing results in complete cessation of respiration in mammalian infants (Harned et al., 1978; Lucier et al., 1979) but, at 2 - 3 months of age, the elicitation results in an alternation of respiration and swallowing (Harned et al., 1978).

In order to determine the effects of increased oropharyngeal stimulation on the BSC of healthy neonates under natural conditions, the BSC of nutritive and non-nutritive swallows during wakefulness were recorded and compared. Given the existing evidence of the effect of sensory stimulation on neonatal physiology, it was hypothesized that the impact of feeding-association sensory stimulation on BSC would be obvious in the neonatal period. It was further hypothesized that this impact would diminish with age since some authors report no obvious impact on adult BSC (Nishino et al., 1985). However, it is acknowledged that there does not appear to be consensus in the literature regarding the effect of nutritive swallowing on the BSC of adults. Some authors report a trend towards increasing post-swallow expiration (Preiksaitis et al., 1992), and others found a significant increase in mid-expiratory swallows (Shaker et al., 1992). Thus, BSC was assessed during wakeful nutritive and non-nutritive swallowing conditions soon after birth and a further nine times until the infants reached 1 year of age.

5.2 Hypotheses 2 and 3

Hypothesis 2: Nutritive BSC will differ from non-nutritive wake BSC within the first 48 hours of life. This difference will be characterized by differing proportional distributions of swallows in at least two respiratory-phase categories, most likely one of which will be P swallow proportions. P swallow proportions will be greater during nutritive than non-nutritive swallowing.

Hypothesis 3: The difference between nutritive and non-nutritive BSC will change within the first year of life such that the impact of feeding is negligible by 1 year of age. At 1 year of age, the proportional distribution of swallows in all respiratory-phase categories will be similar for nutritive and non-nutritive conditions.

5.3 Data Processing and Preparation

All swallows were identified by simultaneous bursts of SEMG activity and swallowing acoustics paired with a cessation in nasal airflow and classified by the primary raters (BK and LR) as II, IE, EE, EI, or P. Behavioural constraints prevented the collection of data during wakefulness on one occasion for two infants. These infants were allocated the percentage frequency of occurrence for all respiratory-phase categories for the relevant condition at the relevant age from another infant determined to be their ‘closest match’ (Elliott & Hawthorne, 2005). The process of identifying the ‘closest match’ infant first involved calculating the sum of the absolute respiratory-phase differences between these two infants and all other infants at each age over the 12 months where no data was missing. Second, as described by Elliott et al., the mean of these differences across all ages was calculated for each infant, and the infant with the smallest overall mean difference was identified as the ‘closest match’ infant. Data collection beyond 1 year of age was not performed due to these behavioural constraints. A random 18 assessments (approximately 18% of all wake and feeding swallows) were reanalysed by the primary rater (BK and LR) and independent raters (LL, BK, and LH) in order to determine intraclass correlation coefficients for intra- and inter-rater reliability, respectively. The effects of respiratory-phase category, age, and condition on coordination were tested using repeated-measures analysis of variance (ANOVA). Respiratory-phase category, age, and condition were entered as within-subject effects. The sphericity assumption for repeated-measures was tested using Mauchly’s test (Mauchly, 1940) and when this assumption was not met the Greenhouse-Geisser correction was applied to the significance

tests. Where significant main or interaction effects were found, they were further explored using LSD tests.

5.4 Results

A total of 19,167 swallows (4,094 non-nutritive and 15,073 nutritive) were analysed (Table 5.1). Intraclass correlation coefficients demonstrated satisfactory inter- and intra-rater reliability for swallow categorization (r = .946 and r = .962, respectively).

Table 5.1 Number of Wake and Feeding Swallows at Each Assessment Age

Age	Wake	Feeding
48 hours	712	1,479
1 week	377	1,777
2 weeks	449	1,778
3 weeks	491	1,722
4 weeks	366	1,508
2 months	467	1,369
3 months	437	1,533
6 months	388	1,415
9 months	250	1,221
1 year	157	1,271
Total	4,094	15,073

During the non-nutritive swallowing condition the distribution of swallows was: EE (35.6%, SE ± 2.2%), P (23.7%, SE ± 1.7%), IE (23.2%, SE ± 1.2%), EI (12.3%, SE ± 1.1%), and II (5.3%, SE ± 0.5%). For the nutritive swallowing condition the distribution was: IE (35.0%, SE ± 2.5%), EE (30.0%, SE ± 1.5%), EI (15.9%, SE ± 2.1%), II (12.9%, SE ± 1.7%), and P (6.2%, SE ± 1.1%). Overall, the majority of swallows were followed by expiration (Table 5.2).

A repeated-measures ANOVA comparing non-nutritive and nutritive conditions revealed an overall respiratory-phase category effect [$F(4, 36) = 44.0$, $p < 0.001$]. Fisher's LSD testing revealed that the proportion of II swallows was lower than that of EE swallows, irrespective

of age and condition (Table 5.2). The repeated-measures ANOVA revealed no overall age effect [$F(1.13, 10.1) = 0.96$, $p = .363$] or condition effect [$F(1, 9) = 1.44$, $p = .261$].

The repeated-measures ANOVA revealed an interaction of respiratory-phase category and age [$F(6.03, 54.3) = 4.59$, $p = 0.001$]. Fisher's LSD testing revealed that the interaction was primarily characterized by a higher proportion of EE than II (at all ages), EI (at all ages except at 1 year), and P (at all ages except at 2 and 4 weeks). There was also a higher proportion of IE than II (at all ages), EI (at all ages), and P (between 2 months and 1 year) (Table 5.2).

The repeated-measures ANOVA also revealed a respiratory-phase category by condition interaction [$F(4, 36) = 29.8$, $p < 0.001$]. Fisher's LSD test showed a lower proportion of P swallows during nutritive than during non-nutritive swallowing conditions.

Finally, the repeated-measures ANOVA revealed a respiratory-phase category by condition by age interaction [$F(6.47, 58.2) = 3.02$, $p = 0.010$). Fisher's LSD tests showed that this interaction was characterized by three phenomena. First, at certain ages, there were higher proportions of II, IE, and EI swallows during nutritive than during non-nutritive swallowing conditions ('A' - 'E' in Figure 5.1). Second, EE swallow proportions were higher in the non-nutritive than nutritive swallowing condition at two ages, but the reverse was true at 48 hours. Third, there were consistently lower P swallow proportions during nutritive than during non-nutritive swallowing throughout the first 6 months of life but not beyond. In summary, the number of respiratory-phase categories subject to a condition effect was low initially, but peaked between 2 weeks and 2 months with the majority of categories affected, and then declined until only one category was affected from 6 months (bottom graph, 'F' in Figure 5.1).

Table 5.2 Proportional Distribution (Mean Percentage and Standard Error Score) of Swallows in Each Respiratory-Phase Category

	Respiratory-phase category									
	II		IE		EE		EI		P	
Age	M	SE	M	SE	M	SE	M	SE	M	SE
48 hours	7.8	2.2	24.2	2.2	37.6	4.0	11.6	2.2	18.7	2.3
1 week	7.7	1.7	27.5	2.0	31.1	3.8	13.8	1.7	19.9	2.7
2 weeks	9.2	1.7	25.0	2.2	31.5	2.0	11.7	1.2	23.1	2.7
3 weeks	6.6	1.4	28.4	1.6	33.8	2.8	9.9	1.9	21.2	1.7
4 weeks	10.2	1.2	27.7	2.0	29.7	2.5	11.4	1.8	21.0	2.9
2 months	11.8	2.4	25.9	2.0	34.1	3.6	14.9	2.4	13.4	2.0
3 months	10.4	2.8	29.0	2.8	30.9	2.5	17.8	2.0	11.9	1.9
6 months	7.2	1.7	33.0	3.1	31.7	3.2	13.6	2.1	14.4	2.7
9 months	8.8	1.8	29.0	3.1	39.8	3.3	17.0	2.5	5.4	1.9
1 year	11.6	2.0	41.4	4.8	27.7	2.8	19.2	2.5	0.2	0.1
Total	9.1	0.9	29.1	1.6	32.8	1.6	14.1	1.3	14.9	1.2

Note: M= mean, SE = standard error, II = inspiration-SA-inspiration, IE = inspiration-SA-expiration, EE = expiration-SA-expiration, EI = expiration-SA-inspiration, P = mid-pause

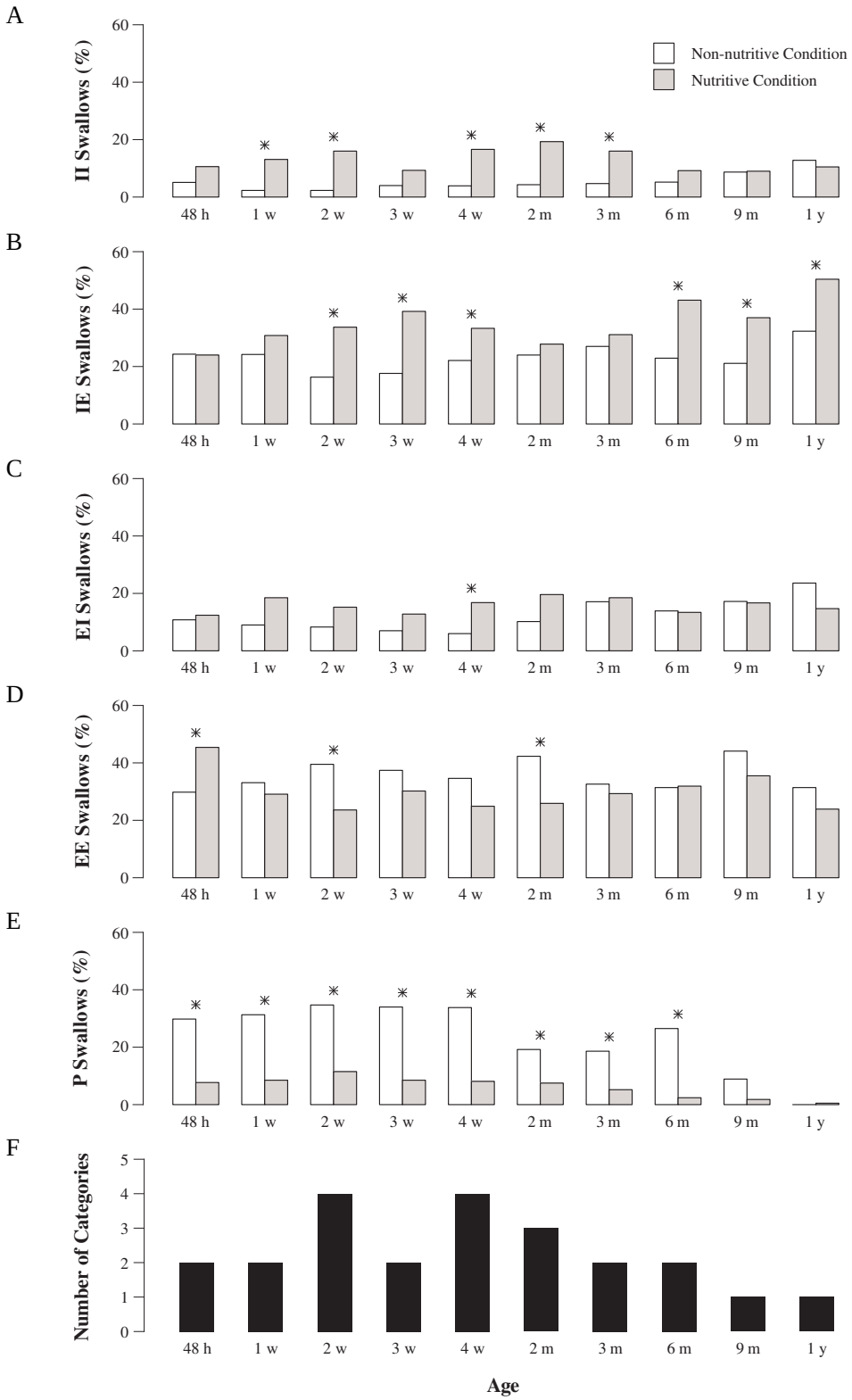


Figure 5.1 Percentage frequency of swallows in each respiratory-phase category during wakefulness (non-nutritive) and feeding (A-E) and the total number of respiratory-phase categories altered by feeding (F).
Note: * = significant condition effect ($p < .05$) determined by Fisher's LSD testing, h = hours, w = week, m = months, y = year

5.5 Discussion

BSC differed between nutritive and non-nutritive swallowing conditions throughout the first year of life in healthy term infants. In particular, the most striking finding was the considerable impact of nutritive swallowing on BSC between the ages of 2 weeks and 2 months (Figure 5.1F). However, the impact of a substantially greater number of feeding swallows than wake swallows (Table 5.1), particularly at these ages, on this effect is unknown. Nonetheless, these results suggest that there may be a 'critical period' during which infants exhibit a greater respiratory response to oropharyngeal stimulation. Similar research in adults has shown no obvious effect of nutritive swallowing on BSC (Nishino et al., 1985) suggesting that the substantial but diminishing effect of nutritive swallowing on BSC in maturing infants is a feature of infant neurophysiology. The present results also indicate that throughout the first year of life the majority of nutritive and non-nutritive swallows are followed by expiration. Post-swallow expiration is also dominant in adults (Hiss et al., 2001; Klahn & Perlman, 1999; Preiksaitis et al., 1992) and, thus, these infants exhibit an adult-like feature of BSC even from birth.

The proportion of mid-pause swallows, although much lower during nutritive than non-nutritive swallowing conditions in the first 6 months, declined gradually with age such that there were virtually none in either condition by 9 months. Although the early and substantial impact of feeding on BSC was expected, a higher proportion of P swallows during nutritive than non-nutritive swallowing was anticipated (Hypothesis 2). This early condition effect on mid-pause swallow proportions could reflect a fusion of *continuous* breathing with nutritive sucking and swallowing in the immature system. This is supported by evidence that preterm infants swallow mainly during respiratory pauses (Mizuno & Ueda, 2003) or in succession without breathing between swallows (Hanlon et al., 1997); both phenomena decline with age. The overall decline in mid-pause swallows with age may also reflect the declining occurrence of respiratory pauses associated with the maturing respiratory system (Richards et al., 1984). With reference to the incidence of respiratory pauses, future research should determine the extent to which respiratory maturation alone accounts for the maturation of BSC. This would require measurements of respiratory function, such as tidal volume and rate, which cannot be calculated by the recording techniques adopted by the present study.

The early impact of nutritive swallowing on BSC suggests that the infant nervous system responds dramatically to the presence of the liquid bolus, particularly between 2 weeks and 2 months. Overall, the proportions of all respiratory-phase categories were subject to a

condition effect at one point or another during the first year. The number of categories subject to this condition effect was maximal during the first month and diminished beyond 6 months. In other words, BSC was most altered by oropharyngeal sensory stimulation associated with bolus ingestion during the neonatal period. These findings suggest that there might be a 'critical period' in the neural development during which otherwise healthy infants may have an exaggerated response to oropharyngeal stimulation.

Perhaps not coincidentally, epidemiological data indicates that there is a 'critical period' for SIDS, with infants between 1 and 6 months at greatest risk (Malloy & Freeman, 2004). This critical period may be the result of apoptosis that occurs after birth which may in turn be responsible for SIDS (Sparks & Hunsaker, 2002). Although the present study was not an investigation into the cause of SIDS, the concurring 'critical periods' and potential contribution of pharyngeal stimulation to SIDS (Jeffery et al., 1999; Lindgren, 1999; Thach, 2000) strengthens the speculated link between non-nutritive swallowing and SIDS (Praud & Reix, 2005). Failure to resume respiration after a non-nutritive swallow, in response to secretions or reflux, may be the result of impaired maturation of suprabulbar regulation. This is supported by the association between premorbid impaired arousal from sleep of future SIDS victims (Einspieler et al., 1988), potential impaired LCR response in SIDS victims during sleep in the prone position (Jeffery et al., 1999), sudden infant death during sleep (Reid, 2001), suprabulbar hypomyelination of autopsied SIDS victims (Kinney et al., 1991), and the potential role of cerebral apoptosis in SIDS (Sparks & Hunsaker, 2002). Since, suprabulbar sites may be responsible for maturing BSC (as described in section 4.5), the critical period for SIDS may be at a time in which suprabulbar maturation plays an important role in regulating BSC.

In the present study, brainstem maturation may account for the declining impact of nutritive swallowing on BSC in the latter stages of the first year (Hypothesis 3). This is supported by a review that concluded that postnatal maturation of a brainstem respiratory centre, the Kolliker-Fuse nucleus, may be the source of more flexible adaptation of sensory processing in the mature individual (Dutschmann et al., 2004). Furthermore, brainstem maturation is involved in the maturation of some of the constituents of BSC. For instance, postnatal brainstem maturation may be at least partially responsible for developmental changes in human respiration (review by Denavit-Saubie et al., 1997) and feeding-related reflexes in mammals (Thexton & Griffiths, 1979). In addition, brainstem maturation coincides with a

decrease in the frequency of prolonged respiratory pauses in preterm infants, suggesting a strong relationship between the two (Henderson-Smart, Pettigrew, & Campbell, 1983).

Age-related changes in the interaction between bulbar and suprabulbar networks may also be responsible for the maturation of the impact of feeding on BSC. Adult brainstem CPGs are influenced by suprabulbar regions (review by Miller, 1999). This is demonstrated by cortical activation of volitional swallowing and cortical influence over the degree of swallowing-related neuromuscular activity (Miller et al., 1997). Similarly, suprapontine structures (above the pons) such as the midbrain and hypothalamus, which are densely connected to the cortex, can also influence respiration (review by Horn & Waldrop, 1998). It is possible that these higher centres are responsible for the integration of afferent information and the ensuing ventilatory adaptation (Horn & Waldrop, 1998). Thus, it is also feasible that pharyngeal sensory stimulation may result in the suprabulbar modulation of respiration. In the developing neonate, higher brain regions may become increasingly active in modulation of CPGs as a result of the myelination of the corticobulbar tract. This tract begins myelinating in the latter stages of gestation and is only well myelinated by the age of 2 years (Sarnat, 1989). Bosma (1986) suggested that in young infants feeding behaviour is primarily brainstem mediated with escalating engagement of suprabulbar structures with increasing age. Thus, increasing suprabulbar regulation of the CPGs controlling BSC may have accounted, at least in part, for the declining impact of nutritive swallowing on BSC in the present study.

It is likely that suprabulbar regions are not entirely quiescent in coordinating breathing and swallowing in healthy neonates. This is supported by evidence that suprabulbar structures are involved in the control of swallowing in mammalian neonates. Specifically, feeding-related cortical areas have been identified in neonatal guinea pigs (Iriki et al., 1988), the feeding abilities of human neonates may be impaired following thalamic damage (Banerjea, Wirbelauer, Trusen, & Speer, 2002) and cortical damage (Sarnat, 1989), and feeding-associated change in cortical activity of human neonates has been reported (Lehtonen et al., 1998).

5.6 Conclusions

Although future research using a greater number of infants should aim to confirm these findings, these results suggest that the BSC of human infants is altered by feeding,

particularly between 2 weeks and 2 months of age. This indicates a possible ‘critical period’ in normal infant neural development during which immature sensorimotor integration can result in an exaggerated efferent response to feeding-related oropharyngeal stimulation. This critical period roughly coincides with an age at which more infants die of SIDS than any other cause (Malloy & Freeman, 2004) and, therefore, offers support for the theories implicating the neonatal response to pharyngeal stimulation as a contributor to SIDS. The magnified neonatal respiratory response to feeding declined with age possibly due to the protracted increase in descending suprabulbar inhibition but more likely due to brainstem maturation.

Chapter 6. Effect of Level of Arousal on Breathing-Swallowing Coordination in the First Year of Life

6.1 Introduction

In the previous chapter a comparison between nutritive and non-nutritive swallowing during wakefulness was made. The marked difference between the two conditions particularly in early infancy, strongly suggested that feeding-related sensory input alters BSC of healthy infants. The impact of pharyngeal sensitivity on BSC can be further examined by comparing non-nutritive swallows performed during wakefulness and sleep. This is because swallowing is not elicited by infused fluids in sleeping mammals (Issa, 1994) and the human adult cough threshold is elevated during sleep compared to wakefulness and in some individuals completely absent (Jamal, McMahon, Edgell, & Fleetham, 1983). Whether these sleep effects are due to decreased sensory processing or motor inhibition remains to be seen (Issa, 1994). Issa (1994) also hypothesized that decreased descending cortical input during sleep is responsible for the failed initiation of swallowing in dogs despite fluid infusion. This is a viable argument given that during the transition into sleep, there is extensive cortical deactivation (reviews b Braun et al., 1997; Hobson & Pace-Schott, 2002). Furthermore, during sleep, particularly NREM sleep, respiration is under fully automated control, whereas during wakefulness, cortical excitation and supramedullary regions can supersede this automated control (Moss, 2005). Thus, sleep provides a condition in which cortical activity is minimal and its comparison to wakefulness provides a suitable paradigm for elucidating potential cortical influence over BSC. A difference in BSC between wakefulness and sleep could therefore be attributed to differing degrees of cortical input, thereby highlighting cortical control.

Certainly, the brainstem is critical in the control of BSC. This is indicated by research that suggests that specific neurons in the ventral respiratory and swallowing groups in the rat brainstem determine the respiratory-phase preceding and following a swallow (Saito et al., 2003). However, multiple respiratory and swallow-related cortical sites have been identified (Colebatch et al., 1991; Davenport & Reep, 1995; Kern, Jaradeh et al., 2001; Martin et al., 2001; Mosier & Bereznaya, 2001) and, thus, it is conceivable that the cortex has some degree of input into the coordination of respiration and swallowing.

Support for the purported cortical influence over BSC comes from two previous studies in the adult population, discussed in section 2.4.2.2. In summary, these studies suggested that BSC during anaesthesia-induced and natural sleep conditions differ to wakefulness as a result of relative decreased arousal and the associated reduction in conscious control (Kelly et al., in press; Nishino & Hiraga, 1991). Specifically, Kelly et al. (Kelly et al., in press) reported an increase in IE swallow proportions and a decrease in EE swallow proportions during sleep. Furthermore, the BSC during quiet sleep in newborn lambs differs to that of active sleep and wakefulness suggesting level of arousal and therefore the centres controlling sleep have some impact on those that are responsible for BSC (Reix et al., 2003). Whether the same would apply to human infants, remains to be seen since there is a paucity of research comparing sleep and wake conditions in human neonates.

Although one previous study monitored BSC during sleep and wake conditions in nine human preterm infants, the data from both conditions were grouped together and analysed as a single entity (Wilson et al., 1981). Miller and Difiore (1995), on the other hand, did compare sleep and wake conditions in human preterm infants, but they investigated the relationship between swallowing frequency and type of apnoea, not the phase of respiration in which swallowing occurred.

The present study is the first to compare BSC under non-nutritive swallowing conditions of sleep and wakefulness to examine the potential cortical role in the BSC of human infants. Evidence from lesion studies in newborn animals that support suprabulbar influence of respiration (review by Neubauer, 1990) and suprabulbar damage in human neonates may result in feeding and swallowing disorders (Sarnat, 1989), thus it was hypothesized that sleep-wake differences in BSC would be evident in healthy term human newborns. It was further hypothesized that differences between sleep and wake conditions would become increasingly apparent as a result of neural maturation. During postnatal development of the CNS, there is substantial synaptogenesis (Huttenlocher & Dabholkar, 1997), synaptic pruning (Sowell et al., 2004), and myelination of the cortex (Gibson, 1991) and corticobulbar tracts (Sarnat, 1989), thus descending suprabulbar (including cortical) input, particularly during wakefulness, is likely to increase as a result.

6.2 Hypotheses 4 and 5

Hypothesis 4: Non-nutritive BSC during wakefulness will differ slightly from that during sleep in neonates within the first 48 hours of life. This difference will be characterized by a higher proportion of IE swallows and/or a lower proportion of EE swallows during sleep.

Hypothesis 5: The impact of sleep on non-nutritive infant BSC will increase with age. The impact will be characterized by differing proportions of swallows in two or more of the following respiratory-phase categories: II, IE, EE, EI, and P swallows.

6.3 Data Processing and Preparation

Swallows were identified by simultaneous bursts of SEMG activity and thyroid acoustics paired with a cessation in nasal airflow by the primary raters and assigned to one of five respiratory-phase categories (II, IE, EE, EI, and P). Behavioural constraints prevented the collection of data during sleep or wakefulness for three different infants on three occasions at different ages. These infants were allocated the percentage frequency of occurrence for all respiratory-phase categories for the relevant condition at the relevant age from another infant that was deemed to be their 'closest match', described in section 5.3 (Elliott & Hawthorne, 2005).

A random 18 assessments (approximately 17% of all sleep and wake swallows) were reanalysed by the primary raters (BK and LR) and independent raters (LL, BK, and LH) in order to determine intraclass correlation coefficients for intra- and inter-rater reliability, respectively. The effects of condition and age on coordination were tested using repeated-measures ANOVA. Condition, age, and respiratory-phase category were entered as within-subject effects. The sphericity assumption for repeated-measures was tested using Mauchly's test (Mauchly, 1940) and when this assumption was not met the Greenhouse-Geisser correction was applied to the significance tests. Where significant main or interaction effects were found they were further explored using LSD tests.

6.4 Results

A total of 7,597 non-nutritive swallows (4,094 wake and 3,503 sleep) were included in the statistical analyses. Intraclass correlation coefficients identified satisfactory inter- and intra-rater reliability for respiratory-phase categorization ($r = .949$ and $r = .977$, respectively).

A repeated-measures ANOVA was performed to determine the effects of age and condition on BSC. This analysis revealed no main effects for age [$F(1.66, 15.0) = 1.31$, $p = .294$] or condition [$F(1, 9) = 0.09$, $p = .770$]. There was, however, a respiratory-phase category effect [$F(4, 36) = 62.8$, $p < .001$]. The Fisher's LSD test revealed significant differences between the following respiratory-phase categories: II (M = 5.1%, SE ± 0.6%) and EE (M = 33.3%, SE ± 1.8%), II (M = 5.1%, SE ± 0.6%) and P (M = 25.6%, SE ± 1.3%), and EI (M = 13.4%, SE ± 1.2%) and EE (M = 33.3%, SE ± 1.8%).

The repeated-measures ANOVA revealed an interaction of age and respiratory-phase category [$F(5.55, 49.9) = 6.12$, $p < .001$]. This interaction was further explored by performing separate repeated-measures ANOVAs for each respiratory-phase category. These revealed no age effects for II [$F(9, 81) = 1.95$, $p = .057$], EE [$F(3.29, 29.6) = 1.44$, $p = .250$], and EI [$F(2.83, 25.5) = 2.71$, $p = .069$] respiratory-phase categories. There were, however, age effects for IE [$F(2.76, 24.8) = 5.02$, $p < .009$] and P [$F(9, 81) = 17.6$, $p < .001$] categories. The LSD test was applied to data on consecutive ages to explore the nature of these age effects. This revealed an increase in IE swallows between 9 months (M = 21.9%, SE ± 4.2%) and 1 year (M = 42.5%, SE ± 7.5%). There were no differences between consecutive ages for P swallows and, hence, the age effect was due to the gradual decrease in P swallows.

It is important to note that there were few swallows in each respiratory-phase category in the latter age groups, particularly for the sleep condition (Table 6.1). Thus, for more robust statistical analysis, data from consecutive ages were amalgamated to obtain a minimum of 10 swallows in each respiratory-phase category for both conditions (Table 6.2). The mean percentage frequency across age groups was calculated for each respiratory-phase category. The amalgamation created four new age-groups; ≥ 48 hours, 1 - 4 weeks (mean of 1, 2, 3, and 4 weeks), 2 - 3 months (mean of 2 and 3 months), and 6 - 12 months (mean of 6, 9, and 12 months). All subsequent statistical analyses reported were performed on the four new age-groups.

Table 6.1 Number of Swallows in Each Respiratory-Phase Category for Both Conditions for Discrete Age-Groups

	Swallowing condition									
	Wake					Sleep				
Age	II	IE	EE	EI	P	II	IE	EE	EI	P
48 hours	33	180	254	73	172	93	271	502	116	430
1 week	10	82	121	36	128	12	69	93	41	235
2 weeks	13	74	170	40	152	22	72	111	45	183
3 weeks	13	89	182	31	176	2	53	94	35	146
4 weeks	17	83	111	25	130	13	70	117	51	165
2 months	27	107	186	48	99	7	21	49	23	35
3 months	22	118	147	73	77	9	28	32	21	23
6 months	18	85	130	55	100	7	20	28	23	19
9 months	22	58	93	45	32	6	22	30	14	5
1 year	19	49	54	35	0	1	18	12	8	1

Note: II = inspiration-SA-inspiration, IE = inspiration-SA-expiration, EE = expiration-SA-expiration, EI = expiration-SA-inspiration, P = mid-pause

Table 6.2 Number of Swallows in Each Respiratory-Phase Category for Both Conditions for Amalgamated Age-Groups

	Swallowing condition									
	Wake					Sleep				
Age	II	IE	EE	EI	P	II	IE	EE	EI	P
48 hours	33	180	254	73	172	93	271	502	116	430
1 - 4 weeks	53	328	584	132	586	49	264	415	172	729
2 - 3 months	49	225	333	121	176	16	49	81	44	58
6 - 12 months	59	192	277	135	132	14	60	70	45	25

Note: II = inspiration-SA-inspiration, IE = inspiration-SA-expiration, EE = expiration-SA-expiration, EI = expiration-SA-inspiration, P = mid-pause

Repeated-measures ANOVAs were performed on the amalgamated data to determine the effects of age and condition on BSC. As for non-amalgamated data, a repeated-measures ANOVA revealed that there was no age effect [$F(1.19, 10.7) = 3.16$, $p = .100$] or condition effect [$F(1, 9) = .416$, $p = .535$] but there was a respiratory-phase category effect [$F(4, 36) = 46.1$, $p < .001$].

Fisher's LSD testing revealed significant differences between the following respiratory-phase categories: II and IE, II and EE, II and P, and EE and EI (Figure 6.1). The means and standard error scores of the each respiratory-phase category during wakefulness and sleep are displayed in Table 6.3.

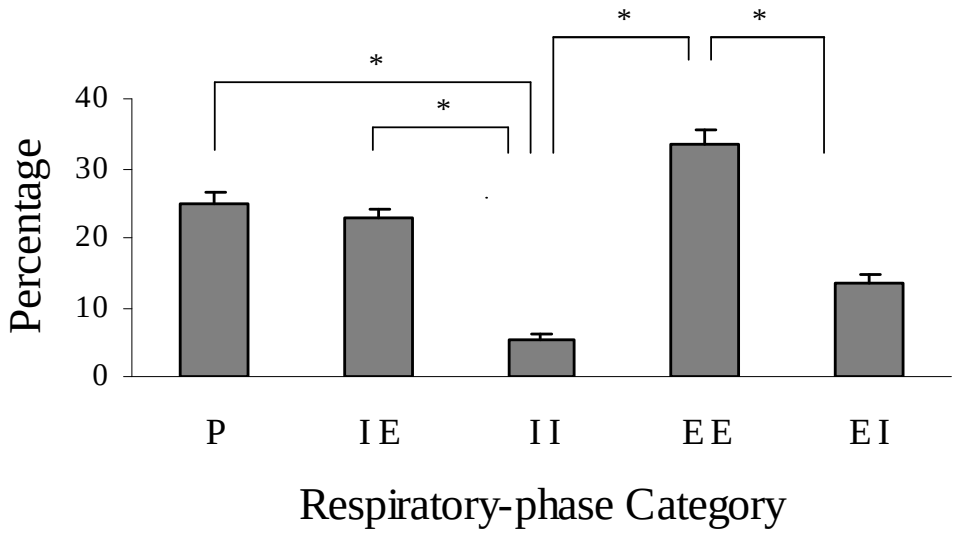


Figure 6.1 Proportional distributions of swallows (mean percentage and standard error score) in each respiratory-phase category.
Note: Results based on amalgamated data, * = significant effect ($p < .05$) determined by Fisher's LSD testing, II = inspiration-SA-inspiration, IE = inspiration-SA-expiration, EE = expiration-SA-expiration, EI = expiration-SA-inspiration, P = mid-pause

The repeated-measures ANOVA revealed an interaction between age and respiratory-phase category [$F(3.65, 32.8) = 9.39$, $p < .001$]. Further exploration of this interaction using Fisher's LSD indicated that the significant respiratory-phase category effects depicted in Figure 6.1 were largely consistent across ages except for the difference between II and P which was no longer apparent in the 6 - 12 month age-group (Figure 6.2). The LSD test also showed that P swallow proportions were greater than EI but only in the first month of life. The dramatic decline in P swallow proportions was also demonstrated by its dominance over IE swallow

Table 6.3 Proportional Distribution (Mean Percentage and Standard Error Score) of Swallows in Each Respiratory-Phase Category for Both Conditions

Respiratory-phase category	Swallowing condition			
	Wake		Sleep	
	M	SE	M	SE
II	5.4	0.6	5.4	0.9
IE	23.8	1.5	22.2	1.9
EE	34.8	2.6	31.8	2.3
EI	12.6	1.2	14.3	1.9
P	23.5	2.2	26.5	1.3

Note: Results based on amalgamated data, M = mean, SE = standard error, II = inspiration-SA-inspiration, IE = inspiration-SA-expiration, EE = expiration-SA-expiration, EI = expiration-SA-inspiration, P = mid-pause

proportions in the 1 - 4 week age-group, and its lower proportional distribution to IE by 6 - 12 months and to EE from 2 - 3 months. Finally, LSD testing showed that EE were greater than IE swallow proportions at 1 - 4 weeks and 2 - 3 months of age.

In order to further assess changes over time within each respiratory-phase category, five separate repeated-measures ANOVAs were conducted for each respiratory-phase category. Age effects were found for II [$F(3, 27) = 4.0$, $p = .018$], IE [$F(3, 27) = 4.87$, $p = .008$], EI [$F(3, 27) = 6.38$, $p = .002$], and P swallow proportions [$F(3, 27) = 23.5$, $p < .001$] but not for EE [$F(3, 27) = .71$, $p = .556$]. The LSD test was applied to data on consecutive ages to explore the nature of these age effects. This revealed a decrease in P swallows between the 1 - 4 weeks and 2 - 3 months. There were no differences between consecutive ages for II, IE, or EI proportions and, hence, the age effect is due to the gradual increases in proportional distribution of these categories (Figure 6.2).

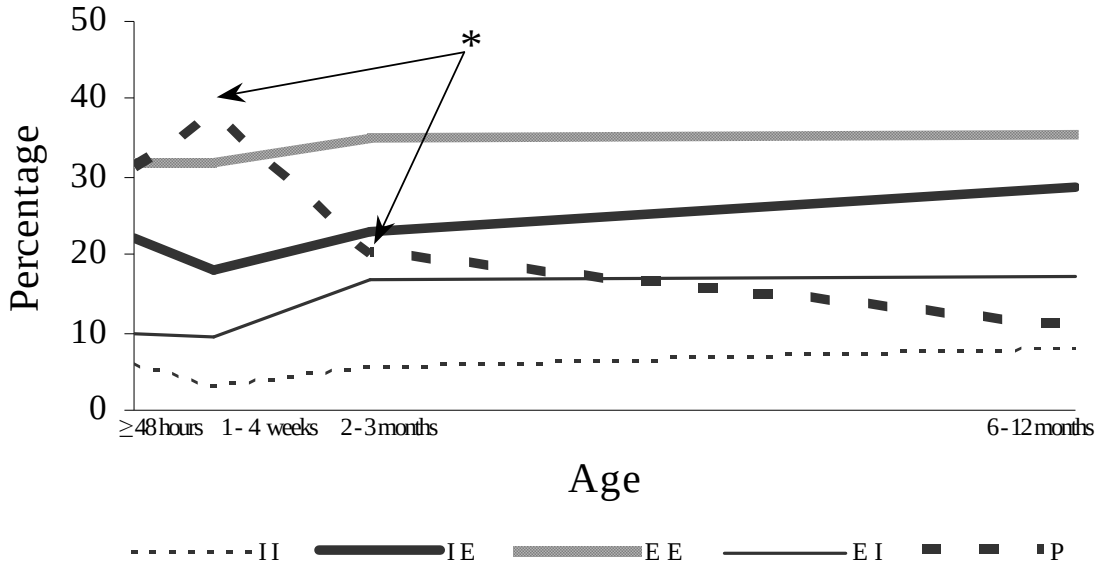


Figure 6.2 Proportional distributions of non-nutritive swallows (during wakefulness and sleep) in each respiratory-phase category for amalgamated age-groups.
Note: The data represented in this graph are not continuous data, but rather data obtained at discrete ages, displayed in this manner for ease of reference, * = significant change between consecutive age groups ($p < .05$), i.e., a decrease in the proportional distribution of P swallows, determined by Fisher's LSD testing; II = inspiration-SA-inspiration, IE = inspiration-SA-expiration, EE = expiration-SA-expiration, EI = expiration-SA-inspiration, P = mid-pause

6.5 Discussion

Non-nutritive BSC during sleep and wakefulness did not differ at any point in the first year of life (Hypotheses 4 and 5 rejected). This may reflect one of three things. First, there was no difference, that is, any increase in the overall level of cortical activity during wakefulness was insufficient to alter infant BSC. Second, the distinction between active and quiet sleep states was not made; the inclusion of both active and quiet sleep states may have prevented the detection of a condition effect given that prior research comparing active and quiet sleep in lambs found a difference in BSC despite no difference between active sleep and wakefulness (Reix et al., 2003). Third, limited sampling may have prevented the detection of a condition effect.

The first explanation is supported by the remarkable similarities of the means and standard error scores between conditions and implies that suprabulbar input into non-nutritive BSC is completely absent, or, at most, minimal and/or inconsistent. However, in the light of sampling issues, this explanation would be strengthened by confirmation of a condition effect in adults. Prior research has not conclusively established whether the condition effect in adults is due to

cortical quiescence alone (Kelly et al., in press; Nishino & Hiraga, 1991). If indeed cortical quiescence influences the BSC of adults, then it is more likely that the results of the present study reflect immature infant cortices. Immature cortices would be unable to contribute substantially to BSC even by 1 year of age. Substantial myelination of the corticobulbar tract continues in the second year of human life (Sarnat, 1989) and cortical organisation beyond that, so it is possible that descending input may increase after 1 year of age, beyond the observation period of this study. The importance of neural maturation for the detection of the condition effect has been highlighted by animal research. Neural maturation in lambs results in the emergence of sleep-wake differences in BSC (Reix et al., 2004). Specifically, the sleep-wake difference evident in newborn term lambs (Reix et al., 2003) was not present in preterm lambs (Reix et al., 2004). However, it must be noted that the non-nutritive BSC of human and animal infants appear to differ and, thus, are likely to differ in terms of susceptibility to condition effects.

In lambs, EE and P swallows occur infrequently and II swallow proportions are higher than any other respiratory-phase category (Reix et al., 2004). In contrast, the human neonates in the present study exhibited high proportions of EE and P swallows, and a very low proportion of II swallows. This human infant pattern changed within the first year and was primarily the result of decreases in P swallow proportions, particularly after the first month of life. By 1 year, IE and EE swallows predominated. These results are in contrast to research by Don and Waters (2003) in which human infants of a mean age of 15.6 weeks were assessed. They reported that 3.9% of swallows occurred during respiratory pauses during sleep compared to 19% for infants between 2 and 3 months of age in the present study. These results differ for two possible reasons. First, they included unhealthy infants who were also not exactly the same age as the infants in the present study. Given the observed maturation of BSC in early infancy, the importance for strict control for age when comparing findings is clear. Second, the present study included in the P respiratory-phase category consecutive swallows between which no respiration occurred, thus the 19% is not only representative of swallows that occurred during respiratory pauses.

The large proportion of P swallows in the neonatal period in the present study may be either peripherally or centrally governed (Praud & Reix, 2005). The argument for peripheral governance is supported by the observation that peripheral stimulation of pharyngeal and laryngeal sensory receptors may induce apnoea and swallowing (Praud & Reix, 2005). The immature gastroesophageal sphincter function may also result in regurgitation in neonates

(Praud & Reix, 2005) and regurgitation is frequently followed by a cessation of respiration and swallowing (Thach & Menon, 1985). Thus, regurgitation may be the source of peripheral stimulation and high occurrence of P swallows in the neonatal period in present study since many of the recordings were completed after feeds. This is supported by animal research that demonstrates the close association between elicited swallows and prolonged respiratory pauses in newborns, with elicited pharyngeal swallows causing complete cessation of respiration (Harned et al., 1978; Lucier et al., 1979).

But the role of central maturation in the decline of P swallow proportions is emphasized by the fact that, by 2 - 3 months of age, the elicitation of pharyngeal swallowing results in the alternation of respiration and swallowing in animals (Harned et al., 1978). In the newborn, central respiratory-swallowing neural interaction in the brainstem during apnoea may trigger swallowing (Praud & Reix, 2005) and maturation of this interaction may result in an increasing fusion of continuous respiration and swallowing and subsequent decline in non-nutritive P swallow proportions. This argument is supported by early fundamental research (Sumi, 1967). The differences in firing patterns of respiratory and swallowing nerves during reflexive swallowing between kittens and adult cats suggests that postnatal maturation involves increasing central differentiation of the neural controls of breathing and swallowing (Sumi, 1967).

A third explanation is that the high proportion of P swallows in the neonates merely reflects the frequent occurrence of respiratory pauses during sleep in term neonates (Ellingson et al., 1982), thereby creating many opportunities for swallowing to occur during a prolonged apnoeic event. It should be noted, though, that the maturation of the frequency of respiratory pauses in the first year of human life appears debatable. According to Ellingson et al. (1982), the rate of respiratory pauses remains stable during the first year, contrary to the reported decline in frequency even within the first 6 months (Adamson et al., 1981b; Richards et al., 1984). Others report an increase in frequency until the age of 6 weeks, followed by a decrease (Guilleminault et al., 1979). The latter pattern appears very similar to our findings that P swallow proportions increase in the neonatal period (albeit statistically non-significant) followed by a significant decrease between 4 weeks and 3 months. Thus, the overall decline in P swallows with age may, to some degree, reflect the declining occurrence of respiratory pauses associated with the maturing respiratory system and/or the increasing likelihood of the fusion of continuous breathing with swallowing in the maturing system.

6.5.1 Limitations

Studying older infants was found to be very challenging given behavioural constraints as also experienced by Litscher et al. (1993). As the infants matured, obtaining sufficient sleep data from daytime recordings was increasingly difficult. This was due to a combination of a decrease in tolerance of equipment placement and unfamiliarity of the laboratory setting, paired with the observed decline in frequency of swallowing and duration of day time sleep. On some occasions no swallows were obtained during approximately 45 minutes of sleep in infants older than 9 months. Wilson et al. (1980) also occasionally observed the phenomenon of absent swallows during quiet sleep in infants. This is substantially different to the swallowing rate of 23 times per hour during sleep in infants between 1 - 34 weeks of age (Don & Waters, 2003). The duration of daytime sleep (Adamson et al., 1981a) and proportion of day- to night-time sleep (Parmelee, Wenner, & Schulz, 1964) decreases notably in the first 4 - 6 months of life. Overnight recordings, although inconvenient for the infants' caregivers, would have yielded more data. However, whether this would have yielded sufficient sleep swallows is still questionable given the association between swallowing and arousal in infants (Sondheimer, 1989).

The declining rate of swallowing and behavioural limitations, particularly for sleep from 6 months of age, restricted the number of swallows obtained. Data from two or more ages had to be amalgamated in order to ensure adequate representation of swallows in each respiratory-phase category within both conditions. Although averaging the data across groups may have reduced variability and therefore potentially also the differences between sleep and wakefulness, this process did not alter the main statistical effects of respiratory-phase category and age. Neither the analysis on discrete age-groups nor that of the amalgamated age-groups revealed condition effects, which strengthens the reliability of the absent condition effect.

6.6 Conclusions

Although the pattern of BSC for non-nutritive swallowing changed over time, there were no emerging sleep-wake differences during the first year of human life. This most likely reflects an absence of cortical control over non-nutritive BSC in infants. However, sampling restrictions prevents confirmation of this and, also, it is not known whether CNS development beyond 1 year would eventually reveal a condition effect. Experimentation on older infants

would raise/encounter many behavioural obstacles, which would make it methodologically difficult. Research confirming a sleep-wake effect in adults would indicate whether further testing on older infants and children would be worthwhile.

Chapter 7. Effect of Feeding on Swallowing Apnoea Duration in the First Year of Life

7.1 Introduction

Although there is much research that confirms the existence of SA in human infants (Bamford et al., 1992; Jeffery et al., 2000; Stevenson & Allaire, 1991; Thach & Menon, 1985; Weber et al., 1986; Wilson et al., 1981), there is little information on the SAD of normally developing infants. Much of the previously reported data were obtained, at least in part, from human preterm (Koenig et al., 1990; Menon et al., 1984) and other paediatric patient populations (Don & Waters, 2003; Wilson et al., 1981). Hanlon et al. (1997) compared term infants (under 1 week of age) and preterm infants. Although they provided longitudinal feeding data on preterm infants from birth to 42 weeks post-conception, the term infants were not assessed beyond the first week of age. Thus, there is no research that determines whether SAD during nutritive swallowing matures in healthy term infants beyond the neonatal period.

Normative data is crucial for the identification of aberrant patterns in the patient population. Since there are links between adequate cardiorespiratory control and efficient feeding (Daniels et al., 1986; Daniels et al., 1988; Daniels et al., 1990; Pinnington, Smith et al., 2000), SAD may be one of the key components of successful integration of breathing and nutritive swallowing. Despite this, it seems that the impact of feeding on SAD has not been directly compared to that of non-nutritive swallowing in healthy term infants. The literature indicates that, in infants, nutritive SAD may be substantially shorter than non-nutritive SAD, at 0.67 s (Hanlon et al., 1997) and 1.03 s (Wilson et al., 1981), respectively.

The need for the successful integration of breathing and non-nutritive swallowing is highlighted in the literature on SIDS. Further to this, immature neural control of BSC may lead to life-threatening events in newborns. There is a possible link between non-nutritive swallowing and SIDS (Praud & Reix, 2005) and between the LCR and SIDS (Jeffery et al., 1999; Lindgren, 1999). Simulation of the LCR elicits a swallow, laryngeal closure, central ‘reflex’ apnoea, hypertension, and bradycardia in infants (Lindgren, 1999; Thach, 2001). Although the LCR is considered to be important in the protection of the airway against ingested or refluxed substances in infants (Richardson, Pernell, & Goding, 1997), elicitation

of the LCR during sleep could potentially lead to death if not accompanied by an increase in arousal (Jeffery et al., 1999). Thus, the relationship between swallowing, airway protection, and apnoea appears crucial to survival and is therefore worthy of further exploration. Furthermore, in Chapter 5 a potential 'critical period' in pharyngeal sensitivity in healthy human infants was reported, as evident by an alteration in the BSC of infants between 2 weeks and 2 months during feeding.

Airway protective reflexes following oral, pharyngeal, and laryngeal stimulation include apnoea and a three-tiered closure response: arytenoid-to-epiglottis contact, closure of the true vocal folds, and closure of the false vocal folds (Miller, 2002). Evidence suggests that swallowing is the primary upper-airway protective mechanism against aspiration of secretions during sleep in human infants (Page & Jeffery, 1998). Research in adult humans and mammals indicates that laryngeal closure during swallowing is critical for the prevention of aspiration (Jafari et al., 2003; Medda et al., 2003). It therefore follows that SAD is a critical component of airway protection during swallowing.

There is evidence that the introduction of a bolus may shorten SAD compared to non-nutritive swallows in adults (Miyazaki et al., 1994; Shaker et al., 1992). However, the effect of bolus introduction on the SAD of infants is unknown, as is the extent of its importance in airway protection in infants.

Comparison of SAD during wakefulness to that during sleep may provide insight into neural control of SAD. The impact of sleep on pharyngeal activity in mammals may be complex: "sleep either reduces the sensitivity of sensory receptors, dampens swallowing centre sensitivity to sensory information, or inhibits motor activity to muscles involved in swallowing" (Issa, 1994, p. 654). Evidence from infant and adult human studies suggests the latter is true. Despite the potential suppression of pharyngeal sensitivity or activity during sleep, airway protective responses are still sensitive to sensory input (Pickens, Schefft, & Thach, 1989). Specifically, the airway protective responses elicited by injection of a liquid bolus into the pharynx of sleeping human infants are altered by the volume of the injected bolus (Pickens et al., 1989). Furthermore, a PET study has shown that the sensory cortices continue to be active during sleep in adults (Braun et al., 1997). The combination of these findings (Braun et al., 1997; Pickens et al., 1989) suggest that pharyngeal sensitivity is at least partially preserved during sleep and that efferent (descending) information and/or associated pharyngeal motor activity rather than sensory activity is likely to be affected by sleep. The

specific effects of sleep on SAD in term infants remains unclear given that research in this area is limited. Although preterm breathing and swallowing during wakefulness and sleep has been monitored by previous authors (Wilson et al., 1981), no comparisons of the SAD for the two conditions were made.

The neural substrates of SAD have yet to be unveiled. Interestingly, adult laryngectomized patients exhibit SA in the absence of a larynx, suggesting that "SA is a central event with its occurrence receiving a dedicated neural command" (Hiss et al., 2003, p. 297) and thus possibly partially distinct from those of swallowing and respiration. Although the preceding chapter indicates that infant non-nutritive BSC is not altered by sleep, whether the same applies to SAD has not yet been established.

The possibility that SAD may be influenced by suprabulbar mechanisms has not been suggested previously. Research indicates that suprabulbar structures influence pharyngeal activity and laryngeal reflexes and, hence, it is possible that these structures can also modify SAD. First, the literature suggests that pharyngeal activity is influenced by the suppression of input from higher brain centres during sleep (review by Isono, 2000). Second, descending hypothalamic input influences laryngeal reflexes in the feline (Dawid-Milner, Silva-Carvalho, Goldsmith, & Spyer, 1995). Thus, if SAD is influenced by descending input from higher brain centres, then SAD will be altered during sleep when the relevant suprabulbar mechanisms are less influential. This alteration might become increasingly obvious as the infant neurological system matures, characterized by an increase in descending suprabulbar input. Maturation (fine-tuning) of SAD in all conditions may be possible given postnatal maturation of similar physiological phenomena, such as mammalian laryngeal airway protective reflexes such as a decrease in apnoea duration of the LCR (review by Thach, 2001), swallowing and feeding behaviours (Rogers & Arvedson, 2005), and respiration (Carroll, 2003). However, it appears that despite the maturation of the aforementioned phenomena, prior research suggests that nutritive and non-nutritive SAD does not change with age. In terms of nutritive SAD, the combined mean of preterm and term infants is 530 ms (Koenig et al., 1990) which is similar to 550 ms of adults (Issa, 1994). Non-nutritive infant SAD is 1.03 s (Wilson et al., 1981) which is also is similar to the reported mean non-nutritive SAD in adults ranging from 860 ms to 1410 ms (Hiss et al., 2001).

The present study aimed to investigate three features of infant SAD: the influence of level of arousal, the influence of liquid bolus ingestion, and the maturation patterns of these influences from birth to 12 months of age.

7.2 Hypotheses 6 and 7

Hypothesis 6: Throughout the first year of life, nutritive SAD will always be shorter than both non-nutritive wake and sleep SAD.

Hypothesis 7: The SAD of nutritive swallows, wake non-nutritive swallows, and sleep non-nutritive swallows will not change with age.

7.3 Data Processing and Preparation

SAD was measured manually by the primary raters (BK and LR) and the mean value for each infant in each condition at every assessment age was entered into the database. The duration of SA could not be measured for P swallows due to the apnoea being imbedded in a prolonged respiratory pause. Similarly, the SADs of individual swallows in consecutive swallow runs cannot be isolated and were thus also excluded from analysis. Behavioural constraints prevented the collection of three data points, once during sleep and twice during wakefulness for three infants of different ages. These missing samples were assigned the SAD value of their ‘closest match’ participant (Elliott & Hawthorne, 2005) at the appropriate assessment age and for the relevant condition. A random 18 assessments (approximately 17% of all wake, sleep, and feeding swallows) was reanalysed by the primary raters (BK and LR) and independent raters (LL, BK, and LH) in order to determine intraclass correlation coefficients for intra- and inter-rater reliability, respectively. The effects of age and condition on SAD were tested using repeated-measures analyses of variance (ANOVA), with both age and condition as repeated-measures factors. The sphericity assumption for repeated-measures was tested by Mauchly’s test (Mauchly, 1940) and when this assumption was not met the Greenhouse-Geisser correction was applied to the significance tests. Where significant main effects were found, they were further explored as pairwise comparisons using LSD tests.

7.4 Results

A total of 19,402 swallows were recorded and analysed. Intraclass correlation coefficients demonstrated satisfactory inter- and intra-rater reliability for SAD measurements (r = .931 and r = .956, respectively). The number of swallows obtained for sleep, wake, and feeding conditions for all assessment ages are shown in Table 7.1. The means and standard error scores of SAD for each assessment age for each condition are shown in Table 7.2. The mean SADs for wake, sleep, and feeding were 784.1 ms (SE ± 29.4 ms), 795.8 ms (SE ± 26.9 ms), and 505.6 ms (SE ± 15.0 ms), respectively. A repeated-measures ANOVA comparing the three conditions revealed a condition effect [$F(2, 18) = 93.7$, $p < .001$] but no overall effect of age [$F(3.54, 31.9) = 0.46$, $p = .740$] or any interaction of condition and age [$F(18, 162) = 0.84$, $p = .653$]. The condition effect was further explored with the completion of two separate repeated-measures ANOVAs comparing feeding SAD to wake and sleep SAD. This showed that feeding SAD was shorter than wake [$F(1, 9) = 137$, $p < .001$] and sleep SAD [$F(1, 9) = 145$, $p < .001$], Figure 7.1.

Table 7.1 Number of Swallows for Sleep, Wake, and Feeding Conditions for All Assessment Ages

	Swallowing condition			
Age	Wake	Sleep	Feeding	Total
48 hours	540	982	1,387	2,909
1 week	249	215	1,614	2,078
2 weeks	297	250	1,570	2,117
3 weeks	315	184	1,590	2,089
4 weeks	236	251	1,365	1,852
2 months	368	100	1,285	1,753
3 months	360	90	1,454	1,904
6 months	288	78	1,383	1,749
9 months	218	72	1,201	1,491
1 year	157	39	1,264	1,460
Total	3,028	2,261	14,113	19,402

Table 7.2 Means and Standard Error Scores of Swallowing Apnoea Durations (in ms) for Each Assessment Age for Each Condition

	Condition					
	Wake		Sleep		Feeding	
Age	M	SE	M	SE	M	SE
48 hours	709.1	31.6	768.8	44.1	498.1	22.0
1 week	833.6	42.5	843.3	57.0	508.7	20.4
2 weeks	806.6	52.4	814.7	57.4	527.5	22.9
3 weeks	754.5	42.4	830.8	35.0	486.8	15.6
4 weeks	785.5	56.9	731.4	51.3	504.9	15.7
2 months	764.8	45.3	751.4	36.4	538.8	24.0
3 months	819.4	87.9	764.0	38.5	508.5	24.4
6 months	779.6	38.7	869.6	67.9	481.0	20.8
9 months	846.8	91.8	757.7	35.9	503.2	29.6
1 year	742.8	67.6	827.6	118.1	498.7	37.6
All ages	784.1	29.4	795.8	26.9	505.6*	15.0

Note: * = significantly different to the overall means of both non-nutritive wake and sleep ($p < .001$), M = mean, SE = standard error.

A repeated-measures ANOVA for SAD during wakefulness revealed no age effect [$F(2.60, 23.4) = 0.64$, $p = .576$]. The maximum difference at any age during wakefulness was only 9.6% of the overall mean. A similar analysis for SAD during sleep also revealed no age effect of age on durations [$F(2.89, 26.0) = 0.70$, $p = .552$]. The maximum difference at any age during sleep was only 8.12% of the overall mean. A repeated-measures ANOVA for SAD during feeding also revealed no age effect [$F(9, 81) = 0.75$, $p = .663$]. The maximum difference at any age during feeding was only 4.9% of the overall mean.

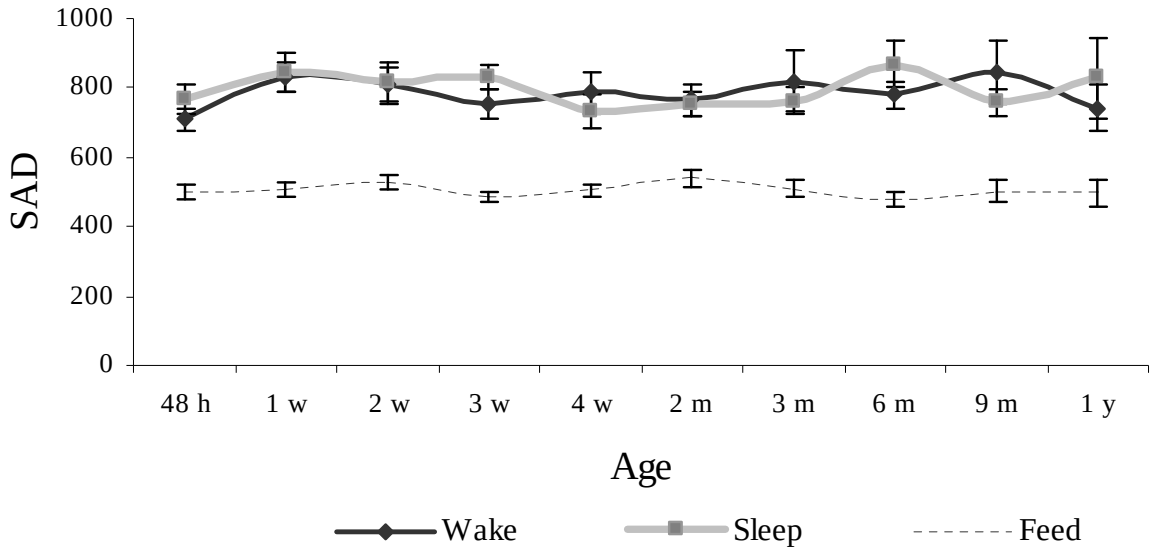


Figure 7.1 The mean duration and standard error scores of swallowing apnoea duration in ms (SAD) during wakefulness, sleep and feeding at each assessment age.
Note: h = hours, w = weeks, m = months, and y = year.

7.5 Discussion

This longitudinal study is the first to demonstrate three important features of infant SAD. First, soon after birth SAD is shorter for nutritive swallows than for both wake and sleep non-nutritive swallows. Second, there is no difference in SAD between wake and sleep non-nutritive swallows. Third, SAD for all three types of swallows (nutritive, non-nutritive wakeful, and sleep swallows) remains essentially unchanged throughout the first year of life.

These findings indicate that feeding-related sensory input has a greater impact on SAD than level of arousal. The absence of a difference between sleep and wake conditions suggests that SAD is impervious to the influences of the suprabulbar centres affected by sleep. This further suggests that SAD is more likely controlled by lower-level (brainstem) and peripheral rather than higher (suprabulbar) neural mechanisms. Given the documented cortical role in respiration and swallowing, these findings support at least partially independent neural controls for SAD, purported by Hiss et al. (2001). The fact that the condition effect exists soon after birth, is maintained throughout the first year of life, and is similar to the condition effect in adults (Miyazaki et al., 1994; Shaker et al., 1992), indicates that it is an innate robust feature of human physiology.

The condition effect observed in the present study suggests that feeding-related sensory input is the key factor in determining SAD, thereby implicating SAD in airway protection. Miyazaki et al. (1994) state that afferent pharyngeal stimulation influences SAD in adults following the observation that adult SAD is longer for non-nutritive than nutritive swallows, and longer following anaesthetization of the pharynx than without. Although the neurophysiology underlying the integration of swallowing and airway defence reflexes is unclear, the numerous connections of the brainstem swallowing-related neurons with other CNS structures suggests they are important in this integration process (Altschuler, 2001). Research has indicated that a branch of the vagus nerve, the SLN, carries the all-important afferent information crucial in the elicitation of airway protective responses such as the laryngeal chemoreflex (review by Thach, 2001). The association between adequate SLN integrity, respiration, and non-nutritive swallowing is further highlighted by research in the paediatric patient population. Infants diagnosed with pathologic apnoea require greater laryngeal sensory stimulation to elicit the laryngeal adductor reflex and are less effective at clearing oral secretions than infants without pathologic apnoea (Thompson, Rutter, Rudolph, Willging, & Cotton, 2005). Given the importance of SLN stimulation in the elicitation of swallowing (Miller, 1999) and the role of the internal branch of the SLN in laryngeal closure, and the prevention of aspiration (Jafari et al., 2003), the SLN clearly plays a critical role in airway protection. Although the present study cannot determine whether the SLN plays a key role in determining SAD, parallels between SAD and this mechanism of airway protection will be made to highlight the complexities of SAD.

The effect of feeding-related sensory stimulation on SAD was not unexpected since sensory input can modify motor output. Laryngeal motor output, especially the force of vocal fold adduction, is reduced following an isolated unilateral lesion of the internal branch of the porcine SLN, which is primarily afferent (Sasaki, Hundal, & Kim, 2005). Some aspects of the biomechanics of swallowing in adults are influenced by the volume of the ingested bolus (Cook, Dodds, Dantas, Kern et al., 1989; Cook, Dodds, Dantas, Massey et al., 1989; Perlman, Schultz, & Van Daele, 1993), highlighting the impact of afferent input on efferent output. Specifically, the duration of the entire pharyngeal swallow (Sonies, Parent, Morrish, & Baum, 1988) and the overall duration of oropharyngeal pressure (Perlman et al., 1993) are less for nutritive than for non-nutritive swallows in adults. Also in adults, the manometric pressure generated by the tongue and pharynx is greater during nutritive than non-nutritive swallows (Cerenko, McConnel, & Jackson, 1989). Whether or not the same principles apply to the biomechanics of infant swallowing remains to be shown. However, these data (Cerenko et al.,

1989; Perlman et al., 1993) and evidence that bolus velocity during swallowing increases with increasing bolus volume (Ergun, Kahrilas, Lin, Logemann, & Harig, 1993) imply that velocity of an ingested bolus is greater than that of a saliva bolus which may account for shorter nutritive swallows and subsequent shorter nutritive SAD.

It is also important to note that respiration rate (Bamford et al., 1992) and ventilation (Mathew et al., 1985) of healthy human term neonates decreases during feeding. This may be in response to the rapid ingestion of fluids and subsequently result in shorter SAD as a means of compensating for ventilatory demands and is echoed in the findings that an increase in respiratory rate is associated with shorter SAD in adult patients with tachypnea (Shaker et al., 1992). Given that the cortex is involved in the modulation of ventilation in response to afferent respiratory input (Horn & Waldrop, 1998), increased ventilatory demands during feeding may have activated the cortex which in turn shortened SAD in order to compensate for the ventilatory demands. This is supported by electrocortical changes in neonates elicited by breastfeeding (Lehtonen et al., 1998).

The results of Lehtonen et al. suggest that feeding-specific electrocortical changes are likely the result of satiety, an increase in vigilance and attention but also affective stimulation (Lehtonen et al., 1998). Feeding-related sensory stimulation is multimodal in nature; gustatory, olfactory, visual, auditory, and somatosensory (Lehtonen et al., 1998), thus it is acknowledged that all these stimuli may have contributed to the feeding effect on SAD in the present study. The influence of sensation on motor response is highlighted by the significance of sensation in protective responses. Airway protective responses are influenced by the presence and characteristics of sensory stimuli detected by receptors in the mucosa of the pharynx (Thach, 1997). SAD is known to increase following topical anaesthesia of the adult pharynx (Miyazaki et al., 1994). Regurgitation is frequently followed by a cessation of respiration and swallowing in infants (Thach & Menon, 1985). Finally, the reflexive protective responses to the injection of water differs to that of saline, for both mice (Khurana & Thach, 1996) and human infants (Davies, Koenig, & Thach, 1988), suggesting that the laryngeal chemoreceptors have a likely role in airway protection from aspiration (Thach, 2001).

It is acknowledged that both bolus size and chemical make-up differed between the feeding and saliva boluses which may account for the differences between nutritive and non-nutritive SAD. Evidence from prior research suggests, however, that the chemical make-up may not be

an independent variable in the present study. The latency of action potentials from the SLN in mammals does not differ for saliva and milk boluses but does for water (Harding, Johnson, & McClelland, 1978). Thus, the condition effect observed in the present study is more likely due to the presence of the ingested bolus than the chemical characteristics thereof.

Although the cortex may have some influence over SAD during feeding, prior research suggests that the feeding-related effect on SAD may be generated at the level of the brainstem. The pattern of sucking in human newborns is altered by peripheral mechanical stimulation, thereby suggesting that the brainstem CPG for sucking is influenced by sensory input (Finan & Barlow, 1998). Brainstem control of SAD is highlighted by the absence of a difference in SAD between sleep and wake conditions. This is because the transition from wakefulness to sleep, particularly NREM sleep, involves widespread cortical deactivation (review by Braun et al., 1997), thus one would expect to see a difference in SAD between sleep and wakefulness if SAD was influenced by higher CNS centres. However, there was no impact of sleep on SAD, implying lower CNS or brainstem mediation of SAD.

The absence of a maturation effect in term infants in the present study is in contrast to the maturation of SAD patterns in preterm infants reported previously. Hanlon et al. (1997) found that regardless of the duration of postnatal experience, preterm infants demonstrate decreasing SAD with age to approximate their term controls. They concluded that neural maturation, and not postnatal experience, determines SAD. It would appear that neural control mechanisms governing SAD are largely mature in term infants soon after birth which again suggests brainstem control over SAD. Brainstem myelination begins well before suprabulbar and cortical regions, with the cortex most likely being fully functional only from 1 year of age in humans (review by Gibson, 1991). It may be appropriate that airway protection mechanisms and those controlling SAD are functional in term infants soon after birth given that feeding commences soon thereafter. Although swallowing occurs in utero (Miller et al., 2003), airway protection mechanisms in the foetus are not crucial since foetal lungs are not primarily used for breathing. Nonetheless, research suggests that the afferents of oral and pharyngeal structures perform optimally even before birth in humans (review by Miller, 2002). This may have important implications for clinical practice. Abnormal SAD may be indicative of neurological immaturity or damage in the paediatric patient population.

The fact that SAD did not change with age in any condition offers support for the previously purported SAD-specific neural control hypothesis, discussed in section 7.1 (Hiss et al., 2003).

SAD appears to be independent of the maturation of similar respiratory- and swallowing-related phenomena suggesting at least partially autonomous neural controls for SAD. The absence of SAD maturation is in contrast to postnatal maturation of breathing (Adamson et al., 1981a; Rusconi et al., 1994), sleep-wake states (review by Peirano, Algarin, & Uauy, 2003), and airway protective responses to SLN stimulation in mammals (Miller & Dunmire, 1976; Park et al., 2001). It also appears that SAD is not influenced by human anatomical maturation during the first postnatal year, including loss of epiglottis-to-soft-palate approximation (Sasaki et al., 1977) and changes in the morphology of the larynx and size of the subglottic space (Eckel et al., 1999). SAD appears relatively unaffected by the maturation of other respiratory and swallowing-related phenomena, suggesting distinct neural mechanisms controlling SAD.

It is also intriguing to note that the SAD of these infants is remarkably similar to the SAD of healthy adults, suggesting that SAD is fully mature soon after birth. For example, the mean SAD of nutritive infant swallows in the present study of 506 ms and the combined mean of preterm and term infants of 530 ms (Koenig et al., 1990), are similar to adult nutritive swallows of 550 ms (Issa, 1994). The mean SAD of 784 ms for non-nutritive swallows during wakefulness is only slightly shorter than the reported mean of 860 ms for non-nutritive swallows in young female adults (Hiss et al., 2001), which suggests slight maturation of non-nutritive SAD during childhood that is not detectable within the first year of life.

The argument that there are neural controls specific to SA (Hiss et al., 2003) is further supported by the likelihood that suprabulbar mechanisms become increasingly involved in feeding (Bosma, 1986; Rogers & Arvedson, 2005; Stevenson & Allaire, 1991) and in nutritive BSC (Chapter 4). If SAD was controlled by higher brain structures, a maturation effect would have at least been observed for nutritive swallowing as a result of encephalization. As this was not observed, this suggests minimal or no overlap between the neural control mechanisms involved in feeding and those involved in SAD.

7.6 Conclusions

SAD is strongly influenced by feeding but not postnatal age or level of arousal in the first year of healthy human life. Although cortical afferent processing and subsequent efferent modulation of SAD is possible, this does not explain the absent sleep-wake and maturation

effects on SAD. The fact that SAD appears largely mature soon after birth suggests that this feature of breathing and swallowing integration is hard-wired and robust. Support for at least partial independence of SAD neural controls from those of respiration and swallowing is supported by differing maturation patterns, and differing susceptibility to certain variables such as level of arousal. Following confirmation of pure brainstem mediation, future comparison to the paediatric patient population may demonstrate that SAD is a useful indicator of brainstem impairment.

PART III: BREATHING-SWALLOWING COORDINATION IN ADULTHOOD

Chapter 8. Methods: Adults

8.1 Participants

Five healthy young males (mean age of 28.2 ± 6.1 years), five healthy young females (mean age of 27.8 ± 5.7 years), five healthy elder males (mean age of 69.6 ± 3.8 years), and five healthy elder females (mean age of 71.6 ± 3.7 years) were recruited by advertisement (Appendix F) following approval by the Canterbury Regional Health Ethics Committee. Written consent was obtained from participants (Appendix G). There was no medical history of myocardial infarct, breathing disorder (e.g., asthma or chronic obstructive pulmonary disorder), swallowing difficulties, severe head and/or neck injury, head and/or neck surgery, sleep disorder (e.g., insomnia or sleep apnoea), neurological disorder (e.g., stroke, multiple sclerosis, Parkinson's disease), gastroesophageal reflux disease, paralysis of the diaphragm, chronic fatigue syndrome, or psychiatric disorder (e.g., anxiety, depression). Potential participants who were taking medication that affected their sleep or level of alertness or attention or were also excluded.

8.2 Participant Tasks

BSC was monitored under three conditions, differing in terms of degree of volitional control over swallowing and degree of overall cortical activity. At one end of this continuum were volitional saliva swallows performed on verbal command. At the other end of the continuum were reflexive saliva swallows immediately preceded by NREM sleep to facilitate minimal cortical activity during the organization of BSC. Between these two conditions on the continuum were spontaneous (naïve) saliva swallows performed during the completion of a distraction task.

Condition A: Twenty spontaneous wake swallows of saliva were performed while participants engaged in a hand-held computer or brain-teaser game. The aim of this task was to distract the participants from concentrating on swallowing, thus providing spontaneous (naïve) saliva swallows while awake. Since the participants were aware that they were participating in research on swallowing, the distraction task was used to ensure naïve swallows were performed. Prior research in which spontaneous swallows were targeted appeared to make no

attempts to distract participants from thinking about their swallowing (e.g., Nishino et al., 1985; Shaker et al., 1992). Deception, as a technique to obtain spontaneous swallows, was not considered appropriate for ethical reasons and to avoid jeopardising researcher-participant trust. In addition, to ensure minimal attentional focus on swallowing, this distraction condition was performed prior to the highly volitional swallowing task (condition B). During condition A, participants were told that the aim of the task was to determine BSC while concentrating on the task at hand, thus it was imperative that they completed the computer game as quickly as possible and obtain a score as high as possible. Participants were in supine position during this task, so that swallows performed in this condition were comparable to those performed in other conditions.

Condition B: Five volitional saliva swallows were performed on command in each of the four positions (in random order) to determine the effect of body position on BSC: supine, prone, on either right or left side (chosen according to the side the participant felt they would most likely sleep), and upright. The first three body positions were chosen so that the swallows were comparable to those performed in conditions A and C. The head remained in neutral position for all participants and positions except for in the prone position due to discomfort and impracticality of neutral head position in which case the head was positioned to the side chosen by the participant.

Condition C: Reflexive saliva swallows were performed overnight while participants slept in whatever positions they felt most comfortable. The number of sleep swallows varied between participants.

8.3 Materials

Simultaneous time-locked recordings of submental muscle activity, thyroid acoustics, and the direction of nasal airflow determined the coordination of breathing and swallowing (refer to Chapter 3 for examples of recordings), and a mercury switch position monitor recorded the body position. These measurements were captured by an integrated hardware-software system (Kay Elemetrics Swallowing Workstation) to allow for the analysis of temporal relationships between measures. Electroencephalography (EEG) was recorded on a separate computer and used off-line to confirm the sleep status of adults. Initiation of data acquisition of the EEG signals and the swallowing workstation was synchronized manually.

8.3.1 Submental Surface Electromyography

SEMG measures the muscle activity associated with the contraction the floor of mouth muscles and reflects a relative measure of hyolaryngeal excursion (Sonies et al., 1996). Thus, submental SEMG was used to detect swallowing (Hiss et al., 2001; Preiksaitis & Mills, 1996). The skin was cleaned using alcohol and men were required to shave prior to commencement of data collection. Cor-gel electrolyte gel was applied to 2 cm silver chloride surface electromyography electrodes (Thought Technology Triode^{TM}). The collective submental muscle group was located by palpation. The two bipolar SEMG electrodes were positioned over this muscle group, with the positive and negative electrodes placed in the midline between the superior border of the thyroid cartilage and the mandibular spine and the reference electrode by default was positioned lateral to the active electrodes (Huckabee & Pelletier, 1999). This electrode array measures the activity of the anterior suprahyoid and lingual muscles (Huckabee & Pelletier, 1999). The electrodes remained in situ for the entire protocol. The submental SEMG signal was amplified, then bandpass filtered (50-220 Hz), rectified, lowpass filtered at 3 Hz, and digitized at 250 Hz.

8.3.2 Laryngeal Microphone

Thyroid acoustics were used to rule out submental SEMG artifact and confirm swallowing onset (Klahn & Perlman, 1999; Preiksaitis & Mills, 1996). Thyroid acoustics were measured using a laryngeal microphone positioned lateral to the thyroid (Takahashi et al., 1994) which was located by palpation and taped in position with standard surgical tape. The microphone was a modified omnidirectional condenser microphone with a sensitivity of -62 ± 3 dB, an impedance of < 2.0 kΩ, and a frequency response of 50 - 12,500 Hz. The microphone was connected to a preamplifier (Rolls mini-mic preamplifier MP13, gain of 6 - 50 dB). The signal from the preamplifier was sampled at 4000 Hz by the Kay Elemetrics Swallowing Workstation via the acoustic channel.

8.3.3 Nasal Cannula

Nasal airflow, using a commercially available adult-size nasal cannula, was recorded to determine the respiratory phase cycle preceding and following each swallow (Hiss et al., 2001; Tarrant et al., 1997) and to determine the duration of SA (Hiss et al., 2001; Martin-

Harris et al., 2005). Nasal prongs were situated at the entrance to each nostril, taped to the cheek using surgical tape and secured firmly around the head. This method has been deemed effective in measuring respiratory events during sleep and more so than nasal thermistors (BaHammam, 2004). Nasal recordings were sampled at 250Hz.

8.3.4 Mercury Switch Position Monitor

Body position was monitored using custom-made mercury switch position monitor secured to a soft elasticized band fitted around the chest with Velcro© at the level of the xiphisternum. A change in body position resulted in a change in the output voltage which correlated to one of four body positions: side-lying (left = 1.02 V, right = 0.69 V), upright (1.55 V), supine (0.35 V) and prone (1.33 V). The mercury switch position monitor was connected to a custom-made sensor box, which also acted as an external battery-operated power source, and the output fed into the auxiliary channel of the Kay Elemetrics Swallowing Workstation. The signal was sampled at 250 Hz.

8.3.5 Electroencephalography

Sleep status was retrospectively confirmed using 4-channel EEG (Curcio, Ferrara et al, 2004). Eight 9 mm bipolar tin EEG electrodes were positioned on the head (according to the international 10-20 EEG positioning system, Figure 8.1): two on the forehead (FP1 and FP2), two over the occipital lobe (O1 and O2), two at central-right position (C3), and two at central-left (C4) (Ficca, Fagioli, & Salzarulo, 2000). The two electrodes at each of the central sites (C3 and C4) were positioned in a rostral-caudal fashion to one another. The EEG montage was bipolar longitudinal (FP1-C3, C3-O1 and FP2-C4, C4-O2). The eight EEG electrodes were connected to Thought Technology EEG Pro/Flex sensors™ which were in turn connected to the appropriate channels of the Thought Technology Procomp Inifiniti™ EEG sensor box. Each EEG channel were sampled at 250 Hz and data stored on an external hard-drive. The EEG data were viewed using a band-pass (Butterworth) IIR filter with a bandwidth of 0.5-40 Hz.

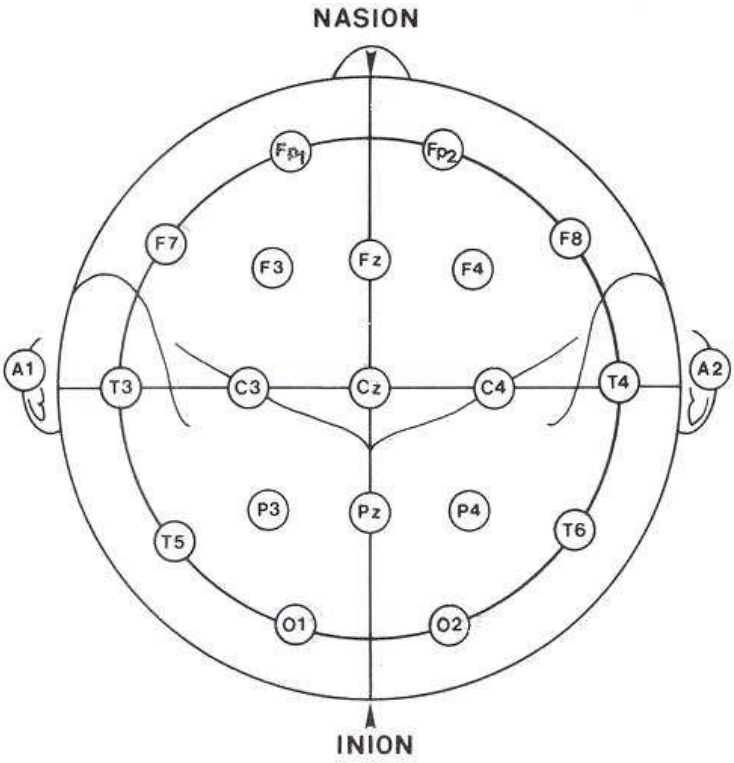


Figure 8.1 The international 10-20 EEG electrode positioning system. The EEG montage used in the present study was bipolar longitudinal (FP1-C3, C3-O1 and FP2-C4, C4-O2). From Duffy, F. H., Iyer, V. G., & Surwillo, W. W. (1989). Clinical Electroencephalography and Topographic Brain Mapping. New York: Springer-Verlag.

8.4 Procedure

Participants were made comfortable on a bed in the Swallowing Rehabilitation Research Laboratory at the Van der Veer Institute for Parkinson's and Brain Research where the submental SEMG electrodes, nasal cannula, microphone, and mercury switch position monitor were fitted and connected to the Kay Elemetrics Swallowing Workstation. The participants were asked to lie comfortably in supine and were given the choice of three types of hand-held games that could be used to engage their attention: computerized hand-held games, hand-held brain-teaser puzzles, and a Rubik's cube. Participants were asked to play their choice of game whilst lying in supine position until instructed to stop. It was emphasized that it was imperative that they perform these tasks as quickly and as accurately as possible so that their attention was focused on the task at hand. Participants were asked to stop after 20 spontaneous swallows were performed.

Once the distraction task was completed, participants were required to swallow saliva when prompted by the examiner in order to ensure that swallows were highly volitional in nature.

Five dry swallows were performed in this manner in each of four positions in random order (totalling 20 swallows): in supine, in prone, on either their right or left side (the side the participant felt they would most likely sleep) and in an upright, sitting position on the bed.

Once the volitional swallowing tasks were completed, their scalp was prepared (demarcated with a felt-tip pen, the skin abraded and cleaned) and the eight EEG electrodes were positioned according to the international 10-20 system. The electrodes were adhered with collodian electrode adhesive and checks were performed to ensure an impedance of less than 5 kΩ on all electrodes. The SEMG electrodes remained in situ during this process and the nasal cannula, laryngeal microphone, and position monitor were repositioned before returning to the bed. Participants were then asked to sleep in whatever positions they wished until they naturally woke the following morning. The commencement of data collection occurred approximately 30 min after the participant had settled in bed and entailed the manual simultaneous initiation of recording by the Kay Elemetrics Swallowing Workstation and the Procomp Infiniti Sensor box.

8.5 Data Analysis

As for the infant data, swallows were identified by simultaneous bursts of SEMG activity and thyroid acoustics paired with a cessation in nasal airflow. All swallows were assigned to one of four respiratory-phase categories based on the phase of respiration preceding and following the SA: inspiration-SA-inspiration (II), inspiration-SA-expiration (IE), expiration-SA-expiration (EE), and expiration-SA-inspiration (EI). Unlike healthy infants, healthy adults do not exhibit prolonged benign respiratory pauses, thus there was no ‘respiratory pause’ (P) swallow category to which adult swallows were assigned. Also unlike infant data analysis, consecutive swallows between which no respiration occurred were excluded from adult statistical analysis since consecutive swallows could not be classified as II, IE, EE, or EI. SAD was measured manually for all swallows using the computer cursor and the mean SAD for each individual for each condition calculated as per the methods detailed for infant swallows (section 3.5).

The amplitude (μV) of the swallow-associated peak SEMG signal was measured manually for all swallows (Crary & Baldwin, 1997; Martin et al., 1994) and a single mean peak value for each individual for each condition was calculated. Since swallowing did not necessarily occur

in all four respiratory-phase categories for every individual in all conditions, a single mean SEMG value for each condition was calculated for each individual based on the means of those respiratory-phase categories that were represented. The peak of the SEMG signal was defined as the highest value of the second (or solitary) peak of the SEMG tracing ('B' in Figure 8.2) that occurred during SA. In the presence of two SEMG peaks, the second peak was chosen in order to minimize the inclusion of oral stage swallowing artifact (i.e., tongue activity) in the analyses. Furthermore, descending cortical input directly or indirectly controls the initial contraction of submental muscles during a volitional swallow (Ertekin & Aydogdu, 2003). The brainstem most likely has control over the later submental muscle contraction (Ertekin & Aydogdu, 2003). Thus, by excluding initial submental SEMG peaks, the hypothesis that the cortex can still influence primarily brainstem/reflexively-generated patterns may be more rigorously tested. In addition to excluding initial submental SEMG peaks only dry swallows were performed to curtail oral stage activity.

The timing of the onset and offset of swallow-related SEMG activity was identified for all sleep swallows (Figure 8.2). Submental SEMG signals can be used to detect the commencement and duration of the pharyngeal swallow (Ertekin & Palmer, 2000). The onset was defined as the time at which the SEMG tracing first increased above 3 μV; a deflection immediately preceding the swallow-related SEMG peak ('A' Figure 8.1). The offset was arbitrarily defined as the time at which the SEMG tracing decreased to below 3 μV, following the swallow-related SEMG peak ('C' Figure 8.2).

The sleep status in both the 20 s prior to the SEMG onset and in the 20 s following the SEMG offset was determined according to conventional sleep staging (Rechtschaffen & Kales, 1968). Thus, the sleep status immediately before and after the swallow was identified as one of three categories: wake or drowsy (wake and stage I, respectively), NREM sleep (stages II - IV), and REM sleep (stage V). In this way, any movement artifact on the EEG signal generated by the swallow was excluded for sleep staging. Given that there is selective reactivation of the medial and posterior prefrontal areas during REM (review by Muzur et al., 2002), only those swallows preceded and/or followed by NREM EEG activity were used for further analysis. Sleep staging according to the Rechtschaffen & Kales scale (1968) has been used in recent respiratory research to provide an estimate of the degree of cortical activation (Boon, Garnett, Bentley, & Milsom, 2004).

8.6 Data Processing, Preparation, and Statistical Analyses

Further details concerning the data processing, preparation, and statistical analyses are outlined in each of the chapters that follow. Statistics were performed using the Statistical Package for the Social Sciences (SPSS, version 11.5, 2002, or version 13.0, 2004) and, unless otherwise specified, a p-value < .05 was taken to indicate statistical significance.

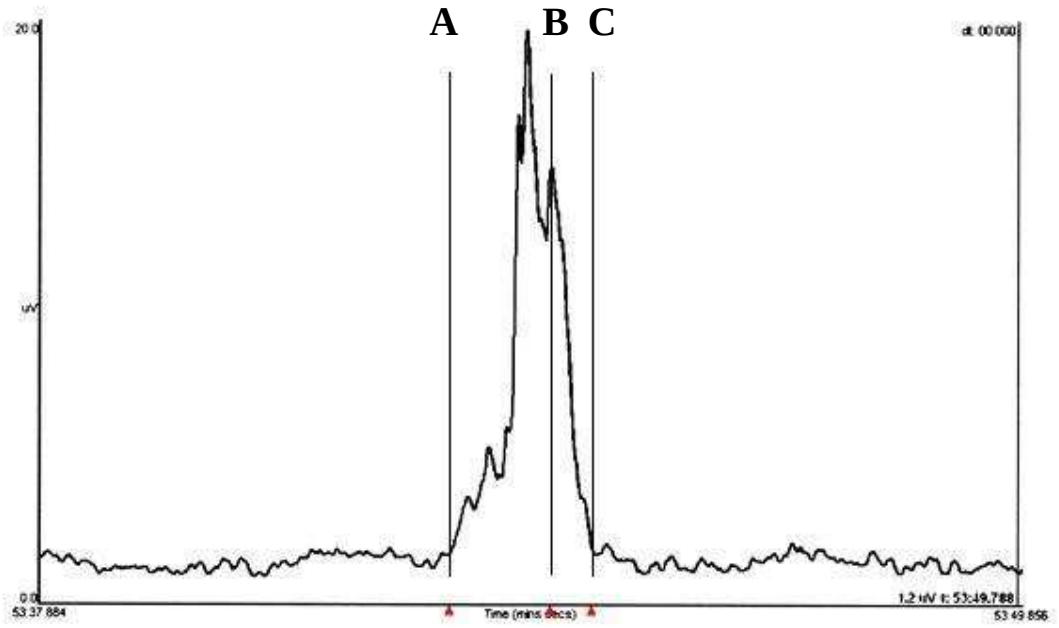


Figure 8.2 The onset (A), peak (B), and offset (C) of swallow-related submental surface electromyographic activity (μV).

Chapter 9. Effect of Body Position on Breathing-Swallowing Coordination in Adults

9.1 Introduction

Postural changes result in changes in upper-airway patency for which the body must compensate to ensure adequate ventilation is maintained (Yates, 2002). On the whole, the effect of body position on respiration, such as lung capacity, compliance, and maximal expiratory pressure, is most apparent between vertical and horizontal positions, with a detrimental effect observed in the latter (Badr et al., 2002; Behrakis et al., 1983; Manning et al., 1999). Animal research confirms that the degree of diaphragmatic shortening also depends on body position in the canine model (Newman, Road, & Grassino, 1986).

These effects of body position on respiration may be largely attributed to biomechanical forces (review by Hoit, 1995), such as the degree of abdominal compression (Badr et al., 2002; Hough, 1984) and diaphragmatic displacement (Manning et al., 1999), the activity of the muscles of expiration (Badr et al., 2002; Hoit, 1995), respiratory recoil mechanisms (Manning et al., 1999), or airway patency (Behrakis et al., 1983; Manning et al., 1999; Yates, 2002).

In terms of swallowing, a change in body position from vertical to horizontal may alter pharyngeal transit times (Ingervall & Lantz, 1973), upper oesophageal sphincter (Castell et al., 1990; Johnsson et al., 1995), and distal oesophageal functioning (Chang et al., 1996). Of particular interest is the finding that the timing of maximal UOS relaxation relative to pharyngeal contraction is increased in the upright compared to supine position (Castell et al., 1990). This demonstrates that swallowing coordination is altered by body position (Castell et al., 1990). It could be argued however, that this is not necessarily an alteration of the coordination or sequencing of neural firing of swallowing but rather the impact of biomechanical changes on the latency of UOS relaxation. Nonetheless, the result of Castell et al. suggests that it is possible that the coordination of other processes such as BSC may also be altered by change in body position.

Position-related biomechanical changes may not be the only mechanism that may alter BSC. It is possible that the changes in respiration as a result of a change in body position may indirectly influence the interaction of respiratory and swallowing brainstem CPGs. Central to the control of swallowing is the NTS, which receives afferent neural information from chemoreceptors and baroreceptors that are sensitive to oxygen and carbon dioxide blood levels and blood pressure, respectively (Miller, 1999). This afferent information is also received by parts of the brainstem that control the diaphragm, the primary muscle involved in inspiration (Miller, 1999). Since body position alters ventilation in animals (Izumizaki, Pokorski, Ishihara, Iwase, & Homma, 2005) and blood pressure in humans (Jones & Dean, 2004), it is therefore conceivable that this is detected by and influences the interaction of respiratory and swallowing CPGs and, hence, alters the pattern of BSC.

The impact of position on BSC has received much less attention than swallowing and respiration. Research comparing the effects of vertical and horizontal body positions on BSC has produced conflicting evidence. McFarland et al. (1994) compared BSC in the upright position to resting on the hands and knees (quadruped position) and found that SA shifted from early to late expiration in the upright position. Unfortunately, they did not report whether or not proportional distribution of swallows in the II, IE, EE, or EI respiratory-phase categories differed between the two conditions. Nonetheless, a shift to late expiration may result in a greater proportion of swallows followed by inspiration (EI). Using the more typical description of BSC, Shaker et al. (1992) found no change in BSC between vertical and horizontal positions. This apparent conflict could reflect different definitions of BSC and/or in the differences in horizontal positions: quadruped (McFarland et al., 1994) and supine (Shaker et al., 1992).

No research has specifically addressed the physiological impact of prone positioning on respiration or swallowing in adult humans. Recent research in mice showed that the respiratory tidal volume is lower in the supine compared to the prone position (Izumizaki et al., 2005) but it is not known whether the same applies to humans. Furthermore, no previous research has specifically examined the influence of gender and position on BSC, although there are gender differences in some temporal features of swallowing relative to SA (Klahn & Perlman, 1999). There are also gender differences in vital lung capacity and respiratory resistance in the upright position that are altered by a change to the supine position depending on the gender, age, and smoking habits of the individual (Michels, Decoster, Derde, Vleurinck, & Vandewoestijne, 1991). As detailed in a comprehensive review, there are many

differences between male and female lung dimensions and structure which may influence lung function and airway behaviour (Becklake & Kauffmann, 1999).

One could speculate that an indirect effect of gender-specific differences in respiratory function on BSC appear only when the respiratory system is maximally challenged, that is, by assuming a horizontal position, resulting in a reduction in lung capacity (Manning et al., 1999). There is consensus in the literature that expiratory performance such as maximal expiratory pressure (Badr et al., 2002), expiratory reserve volume (Behrakis et al., 1983), and forced expiratory volume (Manning et al., 1999), is reduced in horizontal positions compared to vertical. Furthermore, a shift from vertical to horizontal positions has a greater influence on the recruitment of the muscles associated with expiration than that of the diaphragm in order to maintain ventilation when the pulmonary system is challenged by exposure to higher levels of carbon dioxide (Xie, Takasaki, Popkin, Orr, & Bradely, 1991). Thus, it would not be surprising that the respiratory-phase categories subject to a gender-position interaction effect would be only those associated with post-swallow expiration (EE and IE) and that this effect would be most obvious in the horizontal position.

The present study compared BSC in four body positions: three in horizontal plane (supine, side-lying, and prone) and one in vertical plane (sitting upright) in healthy young and elderly adults. It was hypothesized that BSC would be altered by a change in body position, specifically between vertical and horizontal positions, in adults of both age groups. This may have important implications for the neurophysiology of BSC. A position-induced alteration of BSC would imply that BSC is sensitive to peripheral neural feedback rather than being a purely predetermined and invariant brainstem-generated pattern. Since there has been no research on the influence of these four body positions on SAD and swallow-related peak submental SEMG, these two swallowing-related phenomena were also measured and included in the analyses. This comparison is particularly important for determining the neural controls of SAD, given its potential neural independence (Hiss et al., 2003), as discussed in Chapter 7.

9.2 Hypothesis 8

Adult non-nutritive BSC during volitional swallowing will differ between horizontal (supine, side-lying, and prone) and vertical (upright) positions.

9.3 Data Processing and Preparation

Swallows were classified by the primary rater (BK) into one of four categories (II, IE, EE, and EI) and the number of swallows in each respiratory-phase category was calculated for each position for all individuals. SAD and the peak submental SEMG values were also determined for each swallow and the averages of both measures calculated for each position for all individuals.

The data from four participants, one from each age and gender group, selected at random (20% of all volitional swallows) were reanalysed by the primary rater (BK) and independent raters (IL and LT) to calculate intraclass correlation coefficients for intra- and inter-rater reliability on measures of swallow categorization, SAD and peak SEMG. Repeated-measures ANOVA was used to analyse the effect of body position on the number of swallows in each respiratory-phase category. Respiratory-phase category and body position were entered as within-subject factors with age and gender as between-subject factors. Similarly, repeated-measures ANOVAs were used to analyse the effect of body position on SAD and peak SEMG values with body position entered as a within-subject effect and age and gender as between-subject factors. The sphericity assumption for all repeated-measures ANOVAs was tested using Mauchly's test (Mauchly, 1940) and when this assumption was not met the Greenhouse-Geisser correction was applied. Where significant main or interaction effects were found, they were further explored using LSD tests.

9.4 Results

A total of 400 swallows (5 swallows in each of the 4 body positions, for all 20 participants) were recorded and analysed. Intraclass correlation coefficients demonstrated satisfactory inter- and intra-rater reliability for swallow categorization ($r = .904$ and $r = .974$, respectively), SAD ($r = .985$ and $r = .967$, respectively), and peak SEMG values ($r = .985$ and $r = .996$, respectively).

9.4.1 Effect of Body Position on Breathing-Swallowing Coordination

The repeated-measures ANOVA revealed a respiratory-phase category effect [$F(1.96, 31.3) = 56.1$, $p < .001$]. LSD testing revealed that EE swallows occurred most frequently (Figure 9.1). There was no interaction between respiratory-phase category and body position [$F(4.40, 70.3)$

= 2.28, p = .063]. The means and standard error scores of the number of swallows (out of five) obtained in each body position are shown in Table 9.1. There was also no interaction between respiratory-phase category and gender [F(2.0, 31.3) = 0.44, p = .646], respiratory-phase category and age [F(2.0, 31.3) = 0.08, p = .917], respiratory-phase category, body position, and gender [F(4.4, 70.3) = 2.26, p = .065], respiratory-phase category, body position, and age [F(4.4, 70.3) = 1.65, p = .166], or respiratory-phase category, body position, gender, and age [F(4.4, 70.3) = 1.06, p = .387].

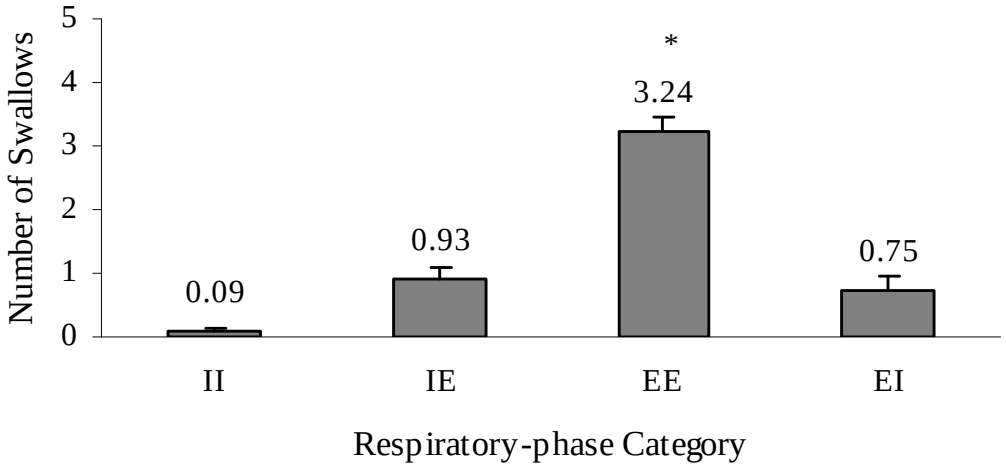


Figure 9.1 The number of swallows (mean and standard error score) in each respiratory-phase category, irrespective of body position, for all participants.
Note: * = significant difference ($p < .05$) determined by Fisher's LSD testing, II = inspiration-SA-inspiration, IE = inspiration-SA-expiration, EE = expiration-SA-expiration, EI = expiration-SA-inspiration

Table 9.1 Mean Number of Swallows (Out of Five) in Each Respiratory-Phase Category in Each Body Position for All Participants

Respiratory-phase category	Body position							
	Prone		Supine		Side-lying		Upright	
	M	SE	M	SE	M	SE	M	SE
II	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1
IE	0.8	0.2	1.3	0.3	1.3	0.3	0.5	0.2
EE	3.4	0.3	3.1	0.3	2.8	0.3	3.7	0.3
EI	0.7	0.2	0.6	0.2	0.9	0.3	0.9	0.3

Note: M = mean, SE = standard error, II = inspiration-SA-inspiration, IE = inspiration-SA-expiration, EE = expiration-SA-expiration, EI = expiration-SA-inspiration

9.4.2 Effect of Body Position on Swallow Apnoea Duration and Peak Submental Surface Electromyogram

The mean SAD value for all swallows was 942.1 ms (SD ± 286.5 ms). Repeated-measures ANOVA showed a body position effect on SAD [F(3, 48) = 2.79, p = .050]. Further exploration of the position effect using LSD testing revealed that the mean SAD of swallows performed in supine was longer than those performed in prone body position (Figure 9.2). There were no effects for age or gender, nor were there interactions of any combinations thereof.

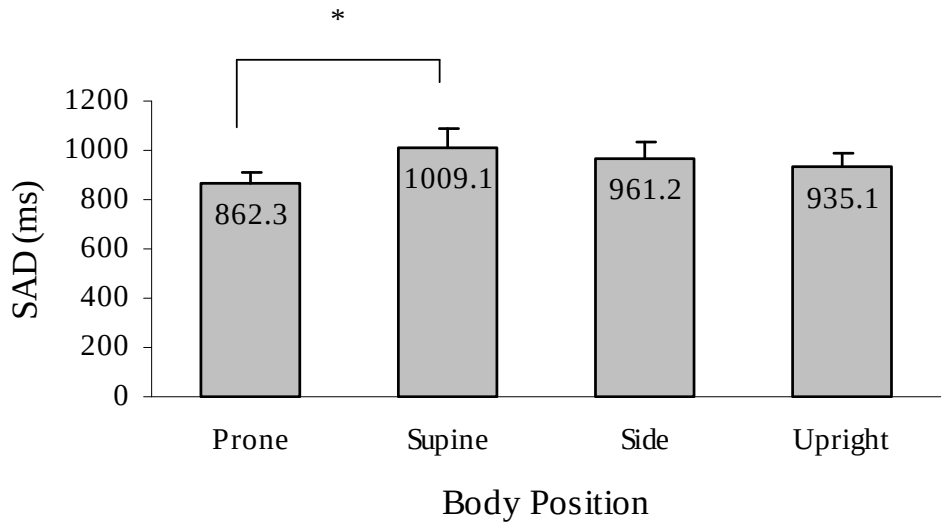


Figure 9.2 Means and standard error scores of swallowing apnoea duration (SAD) for all four body positions, irrespective of gender and age.
Note: * = significant difference ($p < .05$) determined by Fisher's LSD testing.

The mean peak submental SEMG value for all swallows was 41.2 μV (± 21.6 μV). Repeated-measures ANOVA revealed no main effect of position [F(3, 48) = 2.45, p = .075]. There was, however, a position and gender interaction for peak submental SEMG [F(3, 48) = 2.85, p = .047]. LSD testing revealed that the mean SEMG amplitude was higher for males than females in all body positions except for side-lying (Figure 9.3). No age effects or interactions thereof were found.

Figure 9.3 Means and standard error scores for peak submental SEMG values for swallows performed by males and females in all four body positions.
Note: * = significant difference ($p < .05$) determined by Fisher's LSD testing.

9.5 Discussion

The majority of swallows occurred in mid-expiration. This is consistent with prior research indicating that non-bolus volitional swallows occur preferentially in mid-expiration (Preiksaitis et al., 1992). The results demonstrated that body position influenced SAD but there was no strong support for a position effect on BSC. Specifically, SAD was altered by a change in position on the horizontal plane from prone to supine. This may be a consequence of known position-related changes in biomechanical forces on swallowing. Peak submental SEMG was subject to a position and gender interaction. None of these phenomena (BSC, SAD, and peak submental SEMG) were influenced by advancing age. These results suggest that the neural control of BSC is not influenced by changes in respiratory or swallowing biomechanics or peripheral feedback associated with a change in body position in both young and elderly healthy adults. However, it is noted that the absent main effect of position on BSC ($p = .063$) and peak submental SEMG ($p = .075$) should be interpreted with caution given that "there is no sharp border between 'significant' and 'insignificant', only increasingly strong evidence as the P-value decreases" (Moore & McCabe, 1989, p. 486).

The results concur with prior research which demonstrated that BSC during non-volitional swallowing does not change between upright and supine positions (Shaker et al., 1992). McFarland et al. (1994), however, found that a change from a kneeling position to a quadruped position altered nutritive BSC. These positions are similar to the sitting and prone

positions adopted in present study, in which no support for a change in BSC was observed. A possible explanation for this conflict in findings may be due to the inclusion of bolus swallows in the McFarland et al. study as apposed to the present study. Since BSC during bolus and non-bolus swallows may differ (Preiksaitis et al., 1992), the two studies are not comparable and suggests that sensory input from the bolus is perhaps a more important peripheral influence than body position.

The effect of body position on SAD is likely due to the impact of positioning on swallowing given that SAD was sensitive to a change in position only on a horizontal plane. SAD was shorter in prone than in supine position. One likely explanation for this is the comparative impact of these positions on the hyoid bone excursion during swallowing that may indirectly influence SAD. The exact relationship of hyolaryngeal excursion and SAD is not known, however it is conceivable that an elevated hyolaryngeal complex may impinge upon continued respiration. Furthermore, swallowing biomechanics are tightly linked in a largely predetermined pattern that is governed by the brainstem CPG. Thus, it is possible that the neural network governing the duration of laryngeal excursion and those governing SAD interact to synchronize these two activities, supported by research that demonstrates that an increase in one is mirrored by an increase in the other (Martin et al., 1994). The fact that a position effect on SAD but not BSC was observed suggests that SAD and BSC are controlled by independent neural networks or that only SAD is affected by position-related influences on the biomechanics of swallowing.

Further to this, the trajectory of the hyoid excursion during swallowing is characterized by anterior movement and to a lesser extent, superior movement (Ishida, Palmer, & Hiiemae, 2002). Thus, it is conceivable that anti-gravitational forces on the anterior hyoid movement would be maximal in the supine and minimal in the prone position, with side-lying and upright positioning in-between. Additionally, two-dimensional hyolaryngeal excursion is not different between upright and supine positions (Johnsson et al., 1995). Both the present and a previous study (Shaker et al., 1992) demonstrate that SAD also does not differ between upright and supine positions, thereby strengthening the link between hyolaryngeal excursion and SAD. Therefore, if SAD and hyolaryngeal excursion are in fact related, this would offer a feasible explanation for longer SAD in supine than in prone where gravitational forces on anterior hyoid excursion are polarized to the extremes.

Maximal hyolaryngeal excursion is reflected in the peak submental SEMG signals (Sonies et al., 1996). In the present study, peak SEMG was greater for males than females. There are two explanations for this: gender differences in muscle strength and resting hyoid position. First, adult females have less muscle strength than males (Jones, Williams, & Wells, 1986; review by Leveille, Resnick, & Balfour, 2000), which can be attributed to a difference in muscle mass (Hatzikotoulas, Siatras, Spyropoulou, Paraschos, & Patikas, 2004). Second, the male hyoid position at rest is positioned more inferiorly than in females (Ishida et al., 2002). This may account for the earlier initiation of submental SEMG activity in relation to that of SA in males (Klahn & Perlman, 1999) and the greater superior movement of the hyoid bone during swallowing in males, in order to accomplish a similarly effective terminal hyoid position (Ishida et al., 2002). Thus, males may have to recruit greater muscle activity to adequately shift the hyoid, which would explain higher peak SEMG amplitudes in males than females. This argument is supported by the absence of a gender effect in the side-lying position. Given the potential gravitational effect on the anterior-superior hyoid trajectory during swallowing, discussed above, side-lying may be considered the only 'neutral' position out of the four positions included in the present study and for which gender differences in muscle strength would not be apparent.

There was no age effect on peak SEMG. This finding is expected given that evidence for a detrimental effect of age on muscle strength is inconclusive. Jones et al. (1986) found no decrement in arm muscle strength in males or females between 20 and 72 years of age. Others report decreasing muscle strength with age in males and females (Delbaere, Bourgois, Witvrouw, Willems, & Cambier, 2003; Sinaki, Nwaogwugwu, Phillips, & Mokri, 2001). These studies, however, are reporting on *maximum* strength values (Delbaere et al., 2003; Sinaki et al., 2001) whereas the peak submental SEMG values in the present study will undoubtedly represent non-maximal muscle contraction (i.e., *non*-effortful swallowing). This is an important distinction, since there is no age effect on pharyngeal pressure amplitude during non-effortful swallowing (Robbins, Hamilton, Lof, & Kempster, 1992). When oral pressures are compared between non-effortful and effortful swallows, an age effect emerges (Hind, Nicosia, Roecker, Carnes, & Robbins, 2001). Thus, an age effect on the peak submental SEMG of non-effortful swallows would not be expected. Additionally, age was also found not to influence the temporal clustering of respiratory-swallowing events such as the onset of SA relative to the onset of swallowing and maximal hyoid excursion or maximal hyoid excursion itself (Martin-Harris et al., 2003), thus peak submental SEMG, a reflection of

maximal hyolaryngeal excursion (Sonies et al., 1996), is unlikely to change with age under non-effortful swallowing conditions.

There was also no age effect on BSC, which is in agreement with earlier research (Hiss et al., 2001; Selley et al., 1989a) but is in contrast to research indicating that the incidence of pre- and post-swallow respiratory-phase categories differ between older and younger participants (Shaker et al., 1992). However, these results and those of the present study are not directly comparable for two reasons. First, the present study did not perform analyses specifically on pre- and post-swallow categories but rather on four categories determined by the *combination* of pre- and post-swallow respiratory phases. Second, the findings of Shaker et al. (1992) were obtained from a spontaneous swallowing condition unlike the volitional swallowing condition used in the present study. Whether the degree of volitional input into swallowing alters BSC is yet to be established (Kelly et al., in press), but it may explain the contradiction in the findings of the present study and that of Shaker et al. (1992).

Finally, the absent gender effect on SAD is supported by previous research (Martin-Harris et al., 2003), as is the absent age effect (Kelly et al., in press; Shaker et al., 1992). However, one study demonstrated an increase in nutritive SAD with age (Selley et al., 1989a) and another found that non-nutritive SAD of volitional swallows increases with age for women with the opposite effect for men (Hiss et al., 2001). Unlike the present study, the former study included nutritive swallows, and thus may not be directly comparable to the present research. However, the sample sizes in the studies by both Selley et al. and Hiss et al. were substantially larger (33 and 60, respectively), thereby increasing the likelihood of detecting a small but real effect.

9.6 Conclusions

Body position did not alter BSC which suggests that it is impervious to the position-related physiological changes that influence both respiration and swallowing. On the other hand, body position altered SAD and peak submental SEMG values, the latter also being dependent on gender. A shift between the horizontal positions, prone and supine, alters SAD and may be attributed to the position-related impact on hyolaryngeal excursion. Given that SAD, but not BSC, was altered by body position, the argument that the neural controls of SAD are independent of those controlling BSC is strengthened. Males had higher peak SEMG values in all positions (except side-lying) which is not unexpected given the likely impact of the

greater hyoid movement needed in males in these positions. Age did not influence any of these measures (BSC, SAD, and peak SEMG) although a larger sample size may have detected small age-related decrements. Future research should aim to determine the precise reasons for the position effect and gender interaction on SAD and peak submental SEMG values, respectively. The present study offers hypotheses that, through adequate testing, may clarify these reasons.

Chapter 10. Effect of Level of Arousal and Degree of Volitional Swallowing on Breathing-Swallowing Coordination in Adults

10.1 Introduction

The precise neural controls of BSC and SAD are unclear despite these two phenomena receiving much attention in the literature (Clark, 1920; Hirst et al., 2002; Hiss et al., 2001; Kelly et al., in press; Klahn & Perlman, 1999; Martin et al., 1994; Nishino & Hiraga, 1991; Nishino et al., 1985; Paydarfar et al., 1995; Perlman et al., 2000; Preiksaitis et al., 1992; Preiksaitis & Mills, 1996; Selley et al., 1989a, 1989b; Shaker et al., 1992; Smith et al., 1989). BSC may be the result of a complex interaction of multiple subcortical neural networks influenced by descending cortical input. The brainstem is thought to play a substantial role in BSC of the feline (Dick et al., 1993), supported by recent evidence that suggests that brainstem neurones contribute to rodent BSC (Saito et al., 2002; Saito et al., 2003). However, there is evidence supporting the presence of suprabulbar influence in animals (Aleksandrov et al., 2000) and humans (Hadjikoutis et al., 2000; Kelly et al., in press; Nishino & Hiraga, 1991). Furthermore, despite being fundamentally controlled by brainstem CPGs (reviews by Miller, 1999; Sawczuk & Mosier, 2001), both respiration (review by Davenport & Reep, 1995; Horn & Waldrop, 1998) and swallowing (Hamdy, Mikulis et al., 1999; Harris et al., 2005; Huckabee et al., 2003; Kern, Jaradeh et al., 2001; Martin et al., 2001; Martin & Sessle, 1993; Toogood et al., 2005) are independently amenable to cortical influence. Therefore, it is conceivable that BSC, albeit largely brainstem mediated, is also influenced by descending cortical input.

As detailed in the literature review (section 2.2.2), investigating potential suprabulbar influences is difficult for many reasons including the limitations of current neural imaging techniques, the sharing of the neural substrates of respiration and swallowing and the ethical and practical limitations of invasive research on humans. However, one way to investigate the presence of suprabulbar influence, particularly the cerebral cortex, on BSC is to compare BSC and SAD under volitional and reflexive swallowing conditions, a paradigm originally suggested by Kern et al. (2001). Although this paradigm was attempted by previous researchers (Kelly et al., in press; Nishino & Hiraga, 1991; Paydarfar et al., 1995),

methodological flaws prevented the confirmation of suprabulbar influence on either BSC or SAD. Nonetheless, the results of a pilot study suggest that an increase in volitional control results in an increase EE swallow proportions and a decrease in IE swallow proportions (Kelly et al., in press).

The volitional vs. non-volitional swallowing dichotomy is evident in the measurement of submental SEMG during swallowing. The difference between the onset of submental SEMG activity and the laryngeal rise during swallowing is less for non-volitional than volitional swallowing conditions (Ertekin et al., 2001). Since the cortex may be involved in the degree of neuromuscular activity of volitional swallowing (Miller et al., 1997), it is hypothesized that peak submental SEMG values would be less during non-volitional than volitional swallowing conditions.

Although the volitional vs. non-volitional paradigm is appealing, creating conditions under which truly reflexive swallows can be elicited is difficult. In the majority of research where ‘reflexive’, ‘spontaneous’, or ‘subconscious’ swallowing conditions were evaluated, liquid boluses were administered (Ertekin et al., 2001; Nishino et al., 1985; Paydarfar et al., 1995) and/or participants were awake (Ertekin et al., 2001; Martin et al., 2001; Nishino et al., 1985; Paydarfar et al., 1995; Shaker et al., 1992). Both of these situations are problematic when trying to elucidate suprabulbar contributions to BSC, SAD, and peak submental SEMG, due to the potential impact of bolus ingestion (Preiksaitis et al., 1992; Shaker et al., 1992) and cortical influences associated with increased arousal on these phenomena.

The cortex is thought to be involved in sensory processing during liquid swallowing (Furlong, 2004; Hiraoka, 2004). Furthermore, when comparing saliva and liquid swallowing, a recent EEG study demonstrated that “both the cortical process associated with sensory information of pharyngeal swallowing and the cortical preparatory process of pharyngeal swallowing depend on the type of swallowing task” (Hiraoka, 2004, p. 155). Thus, the inclusion of nutritive swallowing should be avoided. When participants are awake, a degree of anticipation or oral preparation (and therefore cortical activation) cannot be entirely ruled out. The mere fact that participants are awake inherently implies some degree of cortical activation especially when no attempt to distract participants from thinking about their swallowing is made (e.g., Nishino et al., 1985; Shaker et al., 1992). In order to obtain truly valid spontaneous, reflexive, non-volitional swallowing, research participants should not be awake. In infants, comparison between sleep and wake swallowing revealed no difference for either

BSC or SAD (section 6.4), although due to sampling issues (section 6.5.1), confirmation of an absent effect of arousal would be achieved if the same experiment was performed in adults.

Whilst controlling for known variables such as bolus ingestion and level of arousal, the present study provides a much more stringent comparison of BSC between non-nutritive volitional and non-volitional (sleep) swallowing conditions in healthy adults than previously adopted. Sleep, particularly NREM sleep, may provide the ultimate condition of relative cortical quiescence relative to wake given the reduction in global cerebral blood flow (Hobson & Pace-Schott, 2002) and therefore a condition in which voluntary input into BSC, SAD, and submental peak SEMG is eliminated. Further comparison between two non-volitional non-nutritive swallowing conditions, sleep and spontaneous wake, will identify whether arousal alone is sufficient to alter these three features of breathing and swallowing. The overall comparison of non-nutritive swallowing during sleep with spontaneous and volitional swallows during wakefulness provides a continuum of cortical activation upon which cortical contributions can emerge.

10.2 Hypotheses 9 and 10

Hypothesis 9: Adult non-nutritive BSC will differ between non-volitional swallowing conditions that vary in terms of the level of arousal, such as non-volitional swallows performed during wakefulness and those performed during NREM sleep. Specifically, the proportion of IE swallows will increase and the proportion of EE swallows will decrease with decreasing level of arousal.

Hypothesis 10: Adult non-nutritive BSC will differ between swallowing conditions that vary in the degree of volitional input. Specifically, the proportion of IE swallows will increase and the proportion of EE swallows will decrease as the level of volitional control over wakeful swallowing decreases.

10.3 Data Processing and Preparation

Volitional, spontaneous wake, and sleep swallows (defined below) were classified by the primary rater (BK) into one of four categories II, IE, EE, and EI and percentage frequency of occurrence of each respiratory-phase category was calculated for each condition for each

individual. SAD and the peak submental SEMG values were also determined for each swallow and the means of both phenomena were calculated for each condition for each individual.

Due to the marginal effect of body position on BSC demonstrated in the previous chapter, only those swallows performed in a horizontal body position were included for analysis. Thus, the BSC, mean SAD, and peak submental SEMG values of volitional swallows that were performed only in horizontal positions, supine, side-lying, and prone, for each individual were included in the present analysis. Similarly, all sleep swallows and spontaneous wake swallows were also performed in horizontal positions (described in section 8.2). Sleep swallows were identified as those that were preceded by a 20 s epoch of NREM sleep: stages II, III, and IV (Rechtschaffen & Kales, 1968). If substantial movement artifact prevented the scoring of an epoch, the following swallow was excluded from further analysis.

The 20 s EEG epochs preceding the swallows performed in the overnight condition by four participants, one from each age and gender group, selected at random (approximately 20% of epochs), were rescored by the primary rater (BK) and an expert in interpretation of EEG (GC) based on the same conventional scoring system (Rechtschaffen & Kales, 1968). Similarly, the swallows of another four participants, one from each age and gender group, selected at random (approximately 20% of volitional, spontaneous, and sleep swallows) were reanalysed in terms of respiratory-phase categorization, SAD and peak submental SEMG values by the primary rater (BK) and independent raters (IL and LT). These three measures and the EEG epoch scores were then submitted separately to intraclass correlation testing to assess intra- and inter-rater reliability for each measure.

Repeated-measures ANOVA was used to determine the condition effect on the proportional distribution of swallows in the four respiratory-phase categories (BSC). Respiratory-phase category and condition were entered as within-subject effects and age and gender as between-subject factors. Similarly, separate repeated-measures ANOVAs were performed on both SAD and peak submental SEMG values. Condition was entered as a within-subject effect, and age and gender as between-subject factors. The sphericity assumption for all repeated-measures ANOVAs was tested using Mauchly's test (Mauchly, 1940) and when this assumption was not met the Greenhouse-Geisser corrections were applied. Where significant main or interaction effects were found, they were further explored using Fisher's LSD tests.

10.4 Results

A total of 1,047 swallows (300 volitional, 400 spontaneous, and 347 sleep swallows) were recorded and analysed. Intraclass correlation coefficients demonstrated satisfactory inter- and intra-rater reliability for sleep staging (r = .821 and r = .889, respectively), swallow categorization (r = .988 and r = .996, respectively), SAD (r = .967 and r = .951, respectively), and peak submental SEMG (r = .972 and r = .977, respectively).

10.4.1 Effect of Volitional Swallowing on Breathing-Swallowing Coordination

Repeated-measures ANOVA revealed a respiratory-phase category effect [F(1.40, 22.5) = 64.1, p < .001]. LSD calculations revealed that the proportional distribution of EE swallows was higher (mean = 58.6%) than any other respiratory-phase category (II = 2.6%, IE = 15.9% and EI = 22.9%), as depicted in Figure 10.1.

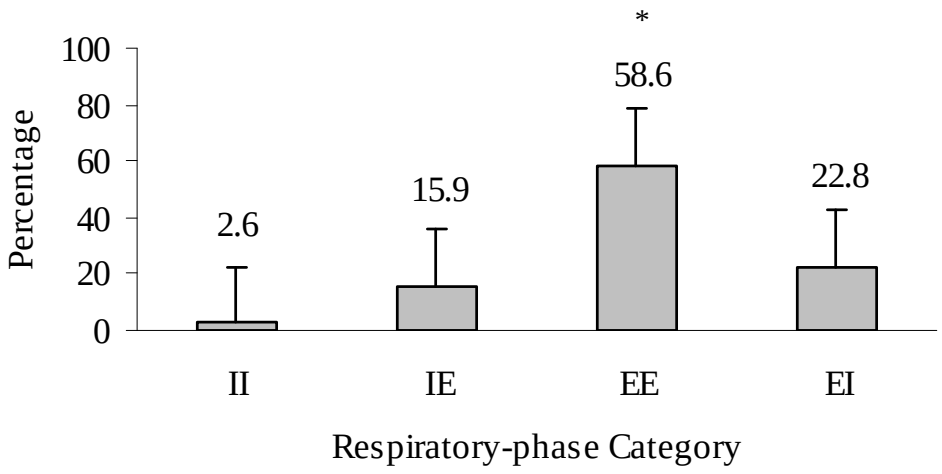


Figure 10.1 Proportional distribution (mean and standard error score) of swallows in each respiratory-phase category irrespective of condition.
Note: * = significant difference (p < .05) determined by Fisher's LSD testing, II = inspiration-SA-inspiration, IE = inspiration-SA-expiration, EE = expiration-SA-expiration, EI = expiration-SA-inspiration

The repeated-measures ANOVA also revealed an interaction between respiratory-phase category and condition [F(3.39, 54.2) = 3.02, p = .032]. LSD testing revealed that volitional and non-volitional swallowing conditions differed in terms of the proportional distribution of swallows in the four respiratory-phase categories (Figure 10.2). Specifically, there was a greater proportion of IE swallows in the volitional than the spontaneous wake condition.

There was also a smaller proportion of EI swallows in the volitional condition compared to spontaneous wake and sleep conditions. But there was no difference between spontaneous and sleep conditions. There were no age or gender effects or interactions of any combination thereof.

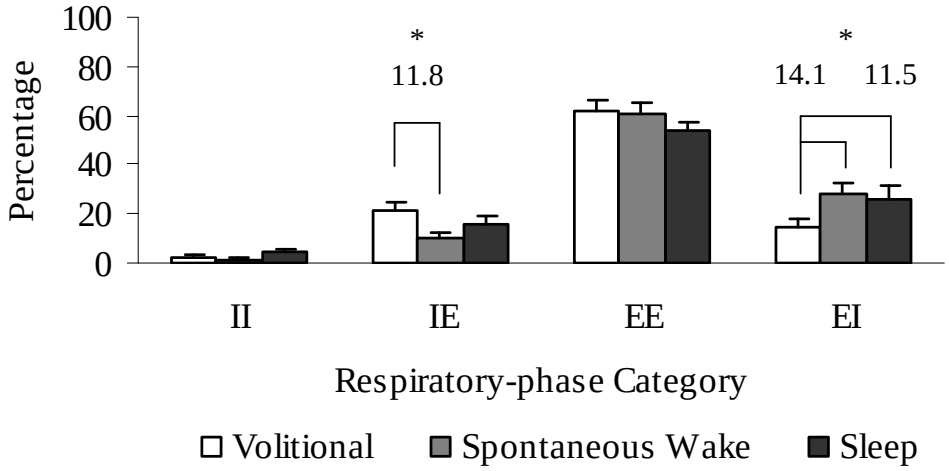


Figure 10.2 Proportional distribution (means and standard error scores) of swallows in each respiratory-phase category for all swallowing conditions.
Note: * = significant interaction ($p < .05$) determined by Fisher's LSD testing, II = inspiration-SA-inspiration, IE = inspiration-SA-expiration, EE = expiration-SA-expiration, EI = expiration-SA-inspiration

10.4.2 Effect of Volitional Swallowing on Swallowing Apnoea Duration and Peak Submental Surface Electromyogram

Repeated-measures ANOVA on SAD showed no condition effect [$F(2, 32) = 2.30$, $p = .112$] or interaction of condition and age or condition and gender. Means and standard error scores of SAD for each age and gender group for all conditions can be found in Table 10.1. Repeated-measures ANOVA on peak submental SEMG values showed a condition effect [$F(2, 32) = 9.89$, $p < .001$] but no interaction of condition and age, or condition and gender. LSD testing revealed that volitionally-initiated swallows produced higher peak SEMG values than non-volitional swallows (Figure 10.3).

Table 10.1 Means and Standard Error Scores of Swallowing Apnoea Duration (ms) for Each Age and Gender Group for All Swallowing Conditions

	Swallowing condition					
	Volitional		Spontaneous wake		Sleep	
Age and gender	M	SE	M	SE	M	SE
Young males	892.8	118.9	738.9	104.8	855.5	137.6
Young females	932.6	118.9	655.8	104.8	828.5	137.6
Elderly males	885.9	118.9	822.8	104.8	1049.0	137.6
Elderly females	1065.7	118.9	991.5	104.8	1004.5	137.6
All participants	944.2	59.5	802.3	52.4	934.4	68.8

Note: M = mean, SE = standard error

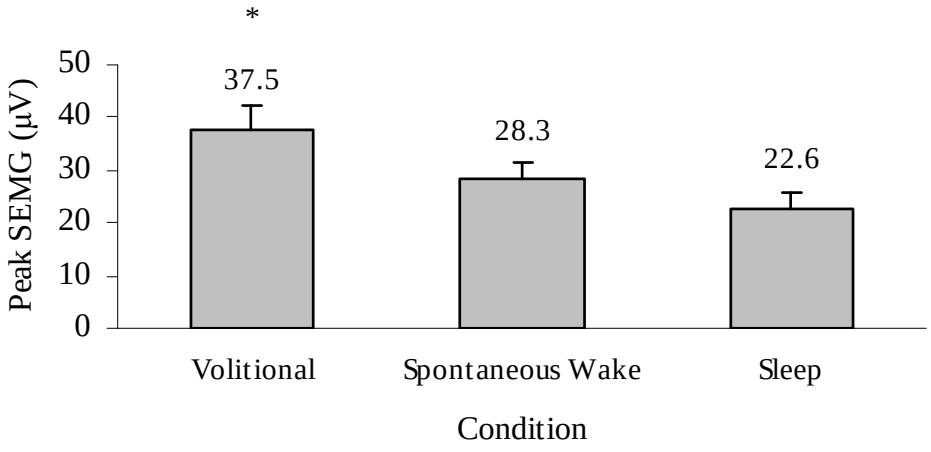


Figure 10.3 Means and standard error scores of the peak submental surface electromyography values (SEMG) for all swallowing conditions.
Note: * = significant difference ($p < .05$) determined by Fisher's LSD testing.

10.5 Discussion

The key finding of this study is that BSC and submental activity differ between volitional and non-volitional swallowing conditions but not between the two non-volitional conditions (spontaneous wake and sleep). This indicates that BSC and submental activity is altered by the degree of volitional input into swallowing but not level of arousal. This in turn confirms the presence of volitional descending cortical control on BSC and submental activity. In

contrast, SAD remained consistent across all swallowing conditions suggesting resistance to suprabulbar influences.

These results support the findings of Chapter 6 in which infant BSC was not influenced by level of arousal. This suggests that the absent effect of sleep on infant BSC is less likely the result of insufficient data, and more likely a true finding. The adult results also suggest that the absent effect of sleep on infant BSC is not the result of inadequate descending cortical influence associated with an immature nervous system. Since volitional swallowing altered adult BSC in the present study, it is more likely that heightened cortical activity associated with wakefulness alone is insufficient to alter BSC and that only the activation of those cortical sites specifically associated with volitional swallowing can influence the brainstem modulation of BSC. Although the present study cannot identify the particular cortical site(s) involved in BSC, it is possible that any of the sites active in both swallowing and respiration may contribute to the process, such as the insular cortex (Davenport & Reep, 1995; Kern, Jaradeh et al., 2001), premotor cortex (Colebatch et al., 1991; Mosier & Bereznaya, 2001), motor cortex (Colebatch et al., 1991; Martin et al., 2001), and supplementary motor cortex (Colebatch et al., 1991; Huckabee et al., 2003; Mosier & Bereznaya, 2001). Since BSC was altered by volitional swallowing, the sites of particular interest are those that may be involved in the initiation or 'planning' of volitional swallowing *prior* to the execution of a swallow such as supplementary motor cortex (Huckabee et al., 2003), cingulate cortex (Wantanbe, Abe, Ishikawa, Yamada, & Yamane, 2004), insular cortex (Dziewas et al., 2003; Wantanbe et al., 2004), and frontal operculum (Dziewas et al., 2003).

Both respiration and swallowing also activate subcortical sites such as the basal ganglia (Fink et al., 1996; Mosier & Bereznaya, 2001), and thalamus (Davenport & Reep, 1995; Mosier & Bereznaya, 2001), which may represent the pathways through which the cortex interacts with the brainstem to coordinate breathing and swallowing. Given that "the cortex generally acts to inhibit the diencephalic areas that facilitate respiration" (Neubauer, 1990, p. 443), it is possible that increased cortical activation during volitional swallowing inhibits the subcortical structures that potentially modulate swallowing and respiratory brainstem CPGs. This may subsequently influence BSC.

Hadjikoutis et al. (2000) hypothesized that damage to the corticobulbar tract may result in reduced suppression of inspiration, evidenced by a propensity for an increase in post-swallow inspiration in patients with damage to this area. This is supported by the results of the present

study that demonstrate an increase in the incidence of one of the post-swallow expiration categories (IE) and a suppression of one of the post-swallow inspiration categories (EI) in the volitional swallowing condition. In general though, swallowing occurred in mid-expiration (58.6%) in all three swallowing conditions. Prior research also found that mid-expiration is the preferred respiratory-phase category for non-bolus swallows (Hiss et al., 2001; Kelly et al., in press; Preiksaitis et al., 1992). This pattern may be attributed to the temporal patterns of activation of specialized brainstem neurones (Saito et al., 2002). The neurones responsible for depressing expiration are active during swallowing, while those responsible for augmenting expiration are activated after swallowing but prior to the activation of the inspiratory neurones (Saito et al., 2002).

Prior researchers have argued that BSC is dependent on level of arousal (Kelly et al., in press; Nishino & Hiraga, 1991): but, under a more stringent experimental design, this was not observed. Thus, the condition effect observed by Nishino and Hiraga was most likely the result of the administration of general anaesthesia. Similarly, the introduction of a liquid bolus in the wake condition must have resulted in the condition effect observed by Kelly et al. This, too, may explain the conflict in terms of the age and gender effects on BSC observed in the pilot study (Kelly et al., in press) that were neither found in the present or prior investigations (Hiss et al., 2001).

The marked effect of sleep on respiratory function is well-documented (review by Krimsky & Leiter, 2005). In fact, sleep is considered to be a state of ‘cardiorespiratory volatility’ (review by Krimsky & Leiter, 2005). Yet, despite the marked impact of sleep on respiration, BSC (and SAD) was not affected by a decrease in the level of arousal in the present study. This difference in susceptibility to sleep, suggests that the respiratory neural controls are partly autonomous to those responsible for BSC and SAD.

Like BSC, peak submental SEMG values differed between volitional and non-volitional swallowing conditions. Submental activity was higher during volitional swallowing, suggesting its susceptibility to volitional cortical input. Since measures were taken to ensure that SEMG values were more likely representative of the pharyngeal stage of swallowing than oral stage artifact (refer to methods section 8.5), these results suggest that the cortex may influence the pharyngeal stage of swallowing. Peak submental SEMG may indirectly represent the pharyngeal stage of swallowing since peak submental EMG (hook wire) values represent the peak contraction of the suprahyoid muscles related to the hyolaryngeal

excursion (Sonies et al., 1996), a component of pharyngeal-stage swallowing. Also “the onset and duration of pharyngeal swallowing can be recorded from the submental/suprahyoid muscles” (Ertekin, 2002, p. 86), thus the results of the present study support the previously purported suggestion that the cortex may indeed influence the pharyngeal stage of swallowing (Hiraoka, 2004).

Increased submental SEMG values during volitional swallowing is not surprising since the cortex can influence the degree of deglutitive neuromuscular activity (Miller et al., 1997), including the modulation of the degree of muscle activity associated with hyoid elevation (Miller, 1999). The cortex may also be involved in sensori-neural processing of the pharyngeal stage of deglutition (Hiraoka, 2004), and may influence the oropharyngeal and even the oesophageal stages of swallowing (Jean, 2001). This is further supported by evidence that the temporary disruption of the primate lateral pericentral cerebral cortex using cold-block microstimulation resulted in decreases in swallow-related EMG amplitudes for the following submental muscles: anterior digastric, geniohyoid, and thyrohyoid (Narita et al., 1999).

Cortical input into SAD, on the other hand, is unlikely since SAD remained roughly the same for volitional and non-volitional swallowing conditions. Research comparing SAD between similar conditions also found no change (Kelly et al., in press). These findings are supported by evidence that the duration of glottic closure is no different for non-bolus volitional, bolus volitional, and reflexive swallows elicited by bolus injection into the pharynx (Shaker et al., 1994).

The absent gender and age effect on SAD is in agreement with some (Kelly et al., in press; Shaker et al., 1992) but not all research (Hiss et al., 2001; Selley et al., 1989a). Similarly, the absence of an age effect on BSC is in agreement with some (Hiss et al., 2001; Selley et al., 1989a) but not all research (Hirst et al., 2002; Kelly et al., in press; Shaker et al., 1992). Likely reasons for the discrepancies were outlined in the previous chapter in which similar findings were observed.

10.6 Conclusions

These findings suggest that BSC and peak submental SEMG are influenced by descending cortical input as evident by their modification educed by volition. More specifically, the absent effect of increased level of arousal suggests that heightened cortical activity associated with wakefulness alone is insufficient to alter BSC and that only the activation of those cortical sites specifically associated with volitional swallowing (e.g., supplementary motor cortex, cingulate cortex, frontal operculum, and insular cortex) are influential. The results of the present study also demonstrate that SAD remained unaltered across all three conditions and is therefore most likely a relatively robust brainstem-mediated function. Finally, age and gender had no impact on BSC, peak submental SEMG, or SAD.

Chapter 11. Effect of Arousal from Sleep on Breathing-Swallowing Coordination: Preliminary Findings

11.1 Introduction

In the previous chapter it was demonstrated that the degree of volitional control over swallowing, and not level of arousal, influences BSC and that this may be attributed to descending cortical influences specific to volition. The sleep swallows included in the previous chapter incorporated those that were immediately preceded by NREM sleep, thereby ensuring relative cortical quiescence during the planning stage of BSC. It was noted during analysis that many of these swallows occurred at the cusp between NREM and drowsiness (Stage I sleep) or wakefulness. In other words, many of the swallows that were initiated in NREM sleep were followed by an increase in arousal.

Evidence suggests that excitability of the human motor cortex is depressed during sleep (Manganotti, 2004). Arousals from sleep entail cortical activation and increased efferent and afferent system excitability (review by Akerstedt et al., 2002). There are many sleep-stage and arousal effects on respiratory- and swallowing-related physiology. During NREM sleep, the phasic activities of pharyngeal and diaphragmatic muscles of healthy humans are altered following momentary electrocortical arousal (Carlson et al., 1994). Normal and brief arousal from overnight sleep is associated with changes in ventilation (Jordan et al., 2003). Swallowing-related primary oesophageal peristaltic movements decrease in frequency with an increase in the depth of sleep (Castiglione et al., 1993). This is supported by an increase in the frequency of swallowing with arousal from sleep (Kahrilas et al., 1987; Lear, 1965; Lichter & Muir, 1975).

Lichter and Muir (1975) found that swallowing often occurs with movement arousals such as facial contortions or eye blinks, during light and REM sleep. These authors suggested that since the frequency of movement arousals are sleep-stage dependent there may be a link between sleep stage, swallowing, and movement arousals (Lichter & Muir, 1975). Interestingly, these movement arousals are most common during REM and light sleep (Lichter & Muir, 1975) during which the cortex is known to be more active than during NREM sleep (Hobson & Pace-Schott, 2002). Waking involves a substantial release of

acetylcholine from the cortex in animals (Celesia & Jasper, 1966). Although the exact role of acetylcholine in swallowing is not clear, research indicates that it plays a principal role in brainstem swallowing activity (Car, Roman, & Zoungrana, 2002) which may explain the association of arousal and an increase in swallowing.

Since arousal is associated with an increase in the level of cortical activity, as well as altered swallow and respiratory behaviour, a pilot investigation was conducted to determine whether BSC differed between swallows associated with arousal and those that were not. The effect of arousal on SAD and peak submental SEMG were also investigated.

11.2 Hypothesis 11

Adult non-nutritive BSC will differ between NREM sleep swallows that are immediately followed by arousal from sleep and those that are not.

11.3 Data Processing and Preparation

Sleep swallows were identified as those preceded or followed by a 20 s epoch of NREM during overnight recording including sleep stages II, III, and IV (Rechtschaffen & Kales, 1968). Since only 4 out of 351 sleep swallows were followed but not preceded by NREM sleep, they were excluded from further analysis. The remaining 347 sleep swallows were all preceded by NREM sleep. Thirty-eight of these swallows (9%) were followed by REM sleep, and were thus also excluded from further analysis. The remaining 309 swallows were divided into two groups. The first group included all those swallows following which NREM sleep state was maintained, henceforth referred to as ‘NREM-sleep swallows’. Since one elderly male and one elderly female did not have any swallows in this first category, they were excluded from the analyses. The second group included the remaining swallows preceded by NREM sleep and followed by an increase in arousal to drowsiness (Stage I sleep) or wakefulness, henceforth referred to as ‘awakening swallows’.

As in the previous two chapters, each swallow was assigned to the four standard respiratory-phase categories (II, IE, EE, and EI) and represented as a percentage of the total number of swallows in the relevant condition for every participant. The mean SAD and mean peak

submental SEMG values for the swallows of each participant were also calculated for each swallow type.

Sleep staging of the 20 s EEG epoch preceding and following all swallows performed of four participants, one from each age and gender group, selected at random (approximately 20%), was rescored by the primary rater (BK) and an expert in interpretation EEG (GC) based on the same conventional scoring system (Rechtschaffen & Kales, 1968). Similarly, the swallows of another four participants, one from each age and gender group, selected at random (approximately 20%) were reanalysed in terms of respiratory-phase categorization, SAD, and peak submental SEMG values by the primary rater (BK) and independent raters (IL and LT). These three measures and the sleep staging scores were then submitted separately to intraclass correlation testing to assess intra- and inter-rater reliability for each measure.

Repeated-measures ANOVA was used to determine the whether the proportional distribution of swallows in the four respiratory-phase categories differed for the two swallow types: NREM-sleep and awakening. Swallow type and respiratory-phase category were entered as within-subject effects and age and gender as between-subject factors. Similarly, separate repeated-measures ANOVAs were performed on both SAD and peak submental SEMG values. Swallow type was entered as a within-subject effect, and age and gender as between-subject factors.

The sphericity assumption for all repeated-measures ANOVAs was tested using Mauchly's test (Mauchly, 1940) and when this assumption was not met the Greenhouse-Geisser corrections were adopted. Where significant main or interaction effects were found, they were further explored using Fisher's LSD testing.

11.4 Results

A total of 301 swallows (167 NREM-sleep and 134 awakening swallows) were obtained from 18 participants (five young males, five young females, four elderly males, and four elderly females). The distribution of the number of swallows in the four respiratory-phase categories is displayed in Table 11.1. Approximately 34% of young adult swallows and 61% of elderly adult swallows were of the awakening type. As per Chapter 10, intraclass correlation coefficients demonstrated satisfactory inter- and intra-rater reliability for sleep staging (r =

.821 and r = .889, respectively). Intraclass correlation coefficients also demonstrated satisfactory inter- and intra-rater reliability for swallow categorization (r = .989 and r = .972, respectively), SAD (r = .959 and r = .904, respectively), and peak SEMG (r = .977 and r = .994, respectively).

Table 11.1 Number of NREM-Sleep and Awakening Swallows in Each Respiratory-Phase Category for Young and Elderly Participants

			Respiratory-phase category			
Swallow type	Age	No. of swallows	II	IE	EE	EI
NREM-sleep	Young	121	5	23	74	19
	Elderly	46	0	7	16	23
	Total	167	5	30	90	42
Awakening	Young	62	8	9	30	15
	Elderly	72	0	9	51	12
	Total	134	8	18	81	27

Note: II = inspiration-SA-inspiration, IE = inspiration-SA-expiration, EE = expiration-SA-expiration, EI = expiration-SA-inspiration

11.4.1 Effect of Arousal from Sleep on Breathing-Swallowing Coordination

Repeated-measures ANOVA revealed a respiratory-phase category effect [$F(1.38, 19.3) = 16.4$, $p < .001$]. LSD calculations revealed a higher proportion of EE swallows (M = 51.3%) than II (M = 3.1%) and IE (M = 15.2%) and a higher proportion of EI swallows (M = 30.3%) than II (Figure 11.1). Most importantly, the repeated-measures ANOVA revealed no interaction of respiratory-phase category and swallow-type [$F(1.54, 21.6) = 0.33$, $p = .666$]. There was, however, an interaction between respiratory-phase category, swallow type, and age [$F(1.54, 21.6) = 4.86$, $p = .025$]. LSD testing revealed a higher proportion of EI swallows for NREM-sleep than awakening swallows for elderly participants (Figure 11.2).

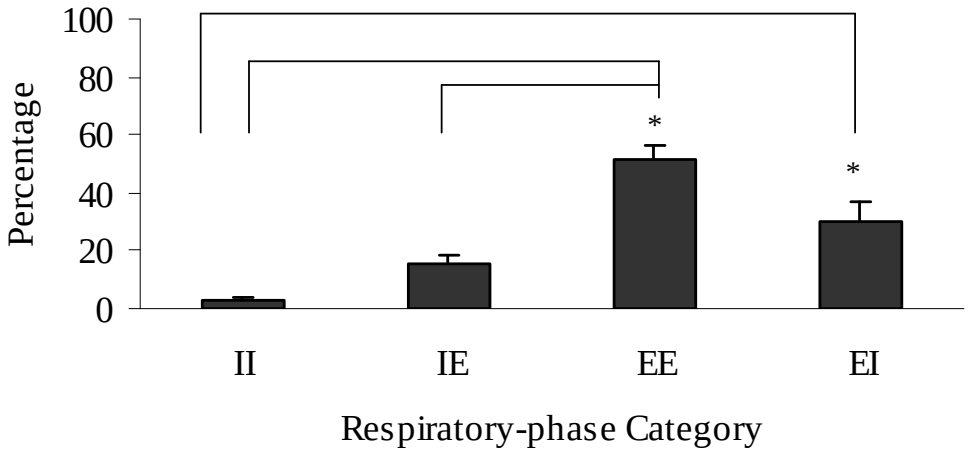


Figure 11.1 Proportional distribution (mean and standard error score) of swallows in each respiratory-phase category.
Note: * = significant difference ($p < .05$) determined by Fisher's LSD testing, II = inspiration-SA-inspiration, IE = inspiration-SA-expiration, EE = expiration-SA-expiration, EI = expiration-SA-inspiration.

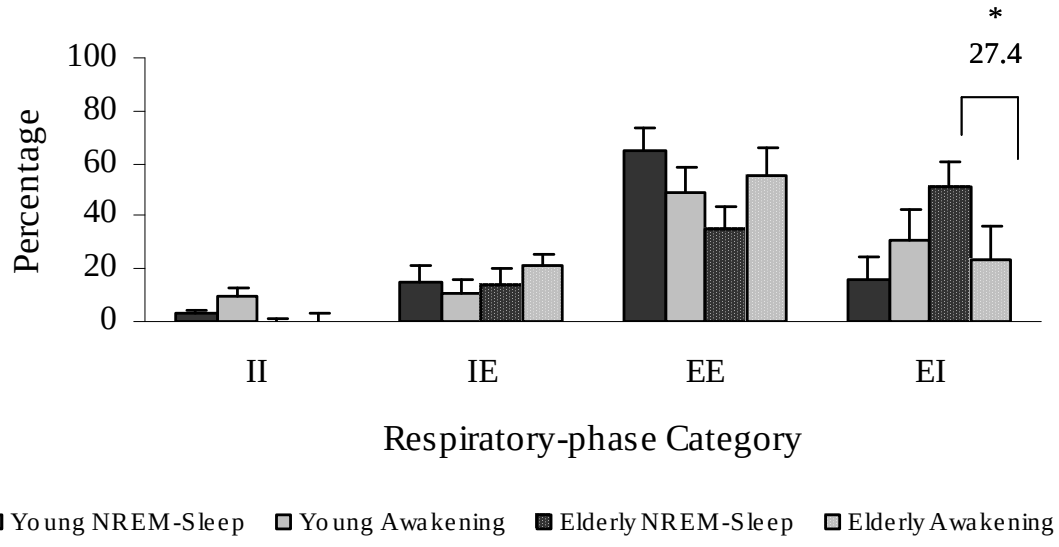


Figure 11.2 Proportional distribution (mean percentage and standard error score) of swallows in each respiratory-phase category for both swallow types and age groups.
Note: * = significant interaction ($p < .05$) determined by Fisher's LSD testing, II = inspiration-SA-inspiration, IE = inspiration-SA-expiration, EE = expiration-SA-expiration, EI = expiration-SA-inspiration

11.4.2 Effect of Arousal from Sleep on Swallowing Apnoea Duration and Peak Submental Surface Electromyogram

Repeated-measures ANOVA on the mean SAD values indicated no effect of swallow type [$F(1, 14) = 1.82$, $p = .199$], however there was an interaction of swallow type and gender [$F(1, 14) = 7.16$, $p = .018$]. LSD testing revealed that SAD of NREM-sleep swallows was longer than that of awakening swallows for males only (Table 11.2).

Repeated-measures ANOVA on the mean peak submental SEMG values showed no swallow type [$F(1, 14) = 0.14$, $p = .717$], or interaction of swallow type and gender, or swallow type and age. Means and standard error scores of peak submental SEMG for each age and gender group for both swallow types are provided in Table 11.2.

Table 11.2 Means and Standard Error Scores of SAD and Peak Submental SEMG for Both Gender Groups

			Swallow type			
			NREM-sleep		Awakening	
Measure	Gender	N	M	SE	M	SE
SAD (ms)	Males	9	1105.0*	104.8	795.5*	98.6
	Females	9	862.3	104.8	964.3	98.6
	All participants	18	983.6	74.1	879.9	69.7
Peak SEMG (μV)	Males	9	22.4	5.6	17.6	3.0
	Females	9	20.3	5.6	22.9	3.0
	All participants	18	21.4	3.9	20.2	2.1

Note: * = significant difference between swallow types ($p < .05$) determined by Fisher's LSD testing, N= number of participants, M = mean, SE = standard error.

11.5 Discussion

This pilot investigation revealed that nearly half (46%) of the swallows preceded by NREM sleep were followed by a period of arousal. This suggests that either swallowing often incites awakening or that awakening elicits swallowing. Either way, it is likely that the depth of the NREM sleep preceding awakening was lighter (i.e., stage II) than the NREM sleep preceding those swallows that were also followed by NREM (i.e., stages III and IV). Confirmation of

this would require more precise sleep-staging. The absence of a change in BSC, despite a likely difference in the depth of the NREM sleep preceding the two swallow types, supports the finding reported in the preceding chapter that BSC is not altered by level of arousal.

Interestingly, but perplexing, the elderly participants exhibited a slight, but significant, difference in BSC between the categories of swallows. Given the absence of an overall effect of level of arousal on BSC and the fact that neither swallow type could have been volitionally initiated, the reason for this age effect is unclear and may be a combination of several factors. One possibility is that the number of swallows obtained for the elderly was less than that for the younger participants, particularly for the NREM-sleep swallows. In fact, the proportion of awakening swallows was much higher for elderly than younger adults (61% vs. 34%), thereby potentially influencing the outcome. Second, although not significant, the young adults showed a higher proportion of EI awakening swallows than NREM-sleep swallows, opposed to the lower proportion observed in the elderly. This bidirectional feature may emphasize the statistical interaction of swallow type and age, especially when the non-significant p-value for the overall swallow type was so high. This switch from a higher to a lower proportion of EI swallows between the younger and older participants may be indicative of age-related degenerative changes in the BSC central pattern generators in the brainstem. Brainstem neural loss associated with the normal ageing process is well documented (Alvarez et al., 2000; Ransmayr et al., 2000; Tang et al., 2001-2002).

It has been purported that CNS degeneration in the elderly accounts for observed differences in some features of sleep, such as eye movement density, between the elderly and the young (Darchia, Campbell, & Feinberg, 2003). An increase in age results in neuronal shrinkage and subsequent reduction in cortical volume, most obvious in frontal and temporal lobes (review by Sowell et al., 2004). Furthermore, a decrease in white matter in the frontal and temporal lobes with advanced age has also been reported (review by Sowell et al., 2004). Thus, it is possible that the arousal pathway between the cortex and brainstem is affected in the elderly, thereby accounting for altered sleep and arousal mechanisms, and potentially BSC.

It is also noteworthy that the two age groups may differ physiologically. Ventilation during NREM sleep is more erratic in the healthy elderly than in the young as a result of vacillating levels of airway resistance (Hudgel, Devadatt, & Hamilton, 1993). The healthy elderly also spend a higher proportion of sleep time in inspiration during NREM sleep but not during

wake (Hudgel et al., 1993). This may account for the effect of swallow type only on the EI respiratory-phase category proportions.

It is also well documented that the sleep architecture of the elderly differs to that of young adults. The elderly spend less time in REM sleep than younger individuals (Ohayon, Carskadon, Guilleminault, & Vitiello, 2004; Vgontzas et al., 2003), something which was observed in the current study during data preparation in which no REM-associated sleep swallows were identified for the elderly. Compared to young adults, the elderly spend less time in NREM slow-wave sleep (Nicolas, Petit, Rompre, & Montplaisir, 2001), sleep less (Vgontzas et al., 2003), and wake more often during the night (Boselli, Parrino, Smerieri, & Terzano, 1998; Floyd, Medler, Ager, & Janisse, 2000). The latter would account for the higher proportion of awakening than NREM-sleep swallows for the elderly.

Finally, older adults spend more time in NREM sleep stage II (Ohayon et al., 2004) and rouse from this stage more often than what is reported for younger adults (Salzarulo et al., 1999). At the beginning of the Discussion it was hypothesized that the depth of the NREM sleep preceding arousal was lighter (i.e., stage II) than the NREM sleep preceding those swallows that were also followed by NREM (i.e., stages III and IV). Given that a higher percentage of the total number of swallows were of the awakening type in the elderly than in the younger adults (61% vs. 34%), a greater proportion of the elderly swallows may have been preceded by a lighter NREM sleep stage. Thus, the difference in BSC between the swallow types in the elderly that was not observed for the younger adults in the present study; may be due to the elderly exhibiting an overall lighter sleep state.

SAD was shorter for awakening than NREM-sleep swallows but only for males. In Chapters 6 and 10 it was demonstrated that SAD remains unaffected by altered level of arousal in infants and adults, respectively, and in the present study there was no overall effect of swallow-type on SAD. Thus, the gender effect observed in the present study is not likely to be the effect of altered level of arousal. Therefore, this finding may also be the result of a combination of factors similar to those that account for the age effect discussed above. Although not significant, females demonstrated an increase in SAD with awakening swallows as apposed to a decrease in males. This bidirectional feature may have resulted in a significant gender interaction effect. Nonetheless, similar gender differences in respiration during arousal from sleep have been documented. Arousal from sleep is associated with greater ventilatory

variability, characterized by hyper- then hypoventilation, for males compared to females (Jordan et al., 2003).

11.6 Conclusions

This pilot study revealed no overall effect of arousal from NREM sleep on BSC, SAD, and peak submental SEMG. These results and those of the previous chapter suggest that BSC and peak SEMG are impervious to slight modifications of the degree of cortical activation, and that only in the event of volitional activation of swallowing is the pattern of BSC altered. Confirmation of an effect of arousal from NREM sleep on the BSC of the elderly and on the SAD of males deserves further investigation with a larger sample size.

PART IV: BREATHING-SWALLOWING COORDINATION ACROSS THE LIFESPAN AND CONCLUDING REMARKS

Chapter 12. Maturation of Awake Non-nutritive Breathing-Swallowing Coordination Across the Lifespan

12.1 Introduction

It is clear from animal research that respiratory- and swallowing-related neurones in the brainstem undergo postnatal maturation (Dutschmann et al., 2004; Haddad & Getting, 1989; Rao et al., 1995, 1997; Schweitzer et al., 1992; Takashima & Becker, 1986; Vincent & Tell, 1999). Yet, this neural maturation is not reflected in patterns of BSC in animals in which BSC during non-nutritive swallows is fully mature at birth (Reix et al., 2004); the BSC of lambs (Reix et al., 2004; Reix et al., 2003) is very similar to adult goats (Feroah, Forster, Fuentes, Lang et al., 2002). There are no previous published data on the maturation of non-nutritive BSC in humans. However the results presented in Chapter 6 demonstrate that non-nutritive BSC does not change with increasing age in this population. Yet, despite this, the non-nutritive BSC of infants still seems to differ from that of adults (Chapter 10). For example, EE and IE swallow proportions were equally prevalent in infant BSC, whereas adults demonstrated a preponderance of EE. Similarly, Wilson et al. (1981) reported that infant non-nutritive swallows can occur in any respiratory-phase category. Although the exact proportional distribution of swallows in each respiratory-phase category is unclear, this seemingly variable pattern appears different to the close association of non-nutritive non-volitional swallows with respiratory-phase categories involving post-swallow expiration in young adults (Shaker et al., 1992). This suggests that, unlike ovines, further maturation must occur between infancy and adulthood in humans.

The possibility that maturation of non-nutritive BSC occurs in humans but not ovines may again highlight the potential role of the cortex in the modulation of BSC. The cortex, a structure which is more developed in humans (Gottesmann, 2004), is likely to become increasingly involved in nutritive BSC in healthy maturing infants (Chapter 4). Cortical input into infant BSC was more obvious during feeding than non-bolus swallowing (Chapters 5 and 6) and is supported by the finding that cortical input into adult BSC is associated with volition, rather than merely increased arousal (Chapter 10). This suggests that cortical input in the maturation of *non-nutritive* BSC may be relatively protracted. Further to this, Ertekin and Aydogdu (2003) argued for evolutionary development of descending cortical influence on the

brainstem swallowing CPG that may be maximal in humans. A more developed cortex in the human model may account for the difference between the BSC during non-nutritive swallowing of newborn lambs (Reix et al., 2004) and that of human neonates discussed in Chapter 6.

In Chapter 6, comparison of wakeful and sleep non-nutritive swallowing revealed that, in general, BSC did not mature in the first year of life. However, the maturational patterns of BSC during wakefulness as a separate entity have not yet been examined. Also, the preceding chapters have described data obtained for infants and adults, separately. Given that the methodologies (see section 12.1.1 below) and, to some extent, the raw data analysis for these two broad age-groups differed across swallowing conditions, a direct comparison was only valid for non-nutritive swallows performed during wakefulness, where both infant and adult participants were engaged in some form of distraction. Furthermore, in Chapter 7 it was shown that the mean SAD of 784 ms for non-nutritive swallows during wakefulness appears to be only slightly shorter than the mean of 802 ms for adults (Chapter 10) and the reported mean of 860 ms for non-nutritive swallows in young female adults (Hiss et al., 2001), which suggests slight maturation of non-nutritive SAD during childhood that is not detectable within the first year of life. In this chapter, data obtained from neonates and one-year-old infants are compared to one another, and then to both young and elderly adults to determine the maturational patterns of BSC and SAD during non-nutritive wakeful spontaneous swallows across the lifespan.

12.1.1 Methodological Differences between Adult and Infant Studies

The methodologies differed for the infant and adult groups in three ways. First, infants were mostly performed wake swallows while lying in supine, a position that could be maintained during sleep, thereby allowing direct comparison between the two conditions. Adults were required to perform volitional wake swallows in a variety of body positions to determine whether body position influenced BSC. It was important to establish whether body position was an independent variable since it could not be controlled for during sleep in adult participants, thereby potentially preventing the comparison of volitional and non-volitional swallowing conditions.

Second, unlike the adult participants, infants could not be asked to perform volitional dry swallows on command. Thus, infant (and not adult) BSC was recorded during nutritive

swallows. Nutritive swallows most closely resemble a highly volitional swallowing task in infants. It was recognized that nutritive swallowing introduced a potential independent variable to the wake condition that could not be reproduced in the sleep condition. This prevented a straightforward comparison between sleep and wake conditions. For this reason the BSC of infants was also recorded during non-nutritive spontaneous swallows while awake and in supine position (when tolerated) during investigator/caregiver interaction. These infant swallows are comparable to the adult non-nutritive spontaneous swallows while awake and in supine position during the completion of a distraction task .

Third, sleep for the infants was subjectively monitored by the author and caregiver and confirmed by failure of the infant to respond to auditory stimuli. The sleep status of adults was confirmed objectively by EEG since behavioural confirmation would have been impractical and unreliable.

12.2 Hypothesis 12

Non-nutritive BSC of non-volitional wake swallows will differ between infants (neonates and one-year-olds) and adults (young and elderly). Specifically, infants are expected to exhibit lower proportions of IE and EE swallows.

12.3 Data Processing and Preparation

Swallows for all participants were identified by simultaneous bursts of SEMG activity and thyroid acoustics paired with a cessation in nasal airflow. The swallows of neonates (< 48 hours) and one-year-olds were assigned to one of five categories: II, IE, EE, EI, and P. Adult swallows were also assigned to II, IE, EE, and EI categories, but not to the P category since adults do not typically exhibit prolonged respiratory pauses. The percentage frequency of occurrence of each respiratory-phase category was calculated for all individuals. The duration of SA was measured manually using a computer cursor and the mean value for each neonate, one-year-old, young and elderly adult was entered into the database. In previous chapters, intra- and inter-rater reliability for swallow categorization and SAD for non-nutritive wake swallows for all age groups has proved satisfactory and are therefore not reported again.

The effects of age on BSC and SAD were tested using repeated-measures ANOVA for the comparison of neonates to one-year-olds and then separate multivariate analyses of variance (MANOVA) to compare neonates to adults, and one-year-olds to adults. This approach was taken given that the assumptions of these statistical tests (repeated-measures ANOVA and MANOVA) prevented the simultaneous comparison of the infants at two different ages to the two groups of adults (Aron & Aron, 2003). Respiratory-phase category and SAD were entered as dependent variables.

It is important to note that the swallows performed during prolonged respiratory pauses and consecutive swallows between which no respiration occurred ('apnoeic swallow runs') were categorized as P swallows in infants. Adults don't typically exhibit respiratory pauses or 'apnoeic swallow runs' and thus occasional consecutive swallows were excluded from adult statistical analysis. Therefore, straightforward comparison between infant BSC (characterized by the proportional distribution of swallows in the 5 respiratory-phase categories) and adult BSC (characterized by 4 respiratory-phase categories) is problematic. For this reason, infant BSC was compared to adult BSC in two ways. First, the 5 infant respiratory-phase categories were compared to adult BSC in which adults were assigned 0 for the P swallow proportion. Second, infant BSC was adjusted[6] to represent the proportional distribution of swallows in the 4 respiratory-phase categories (II, IE, EE, and EI). Since both methods of comparing adult and infant BSC are to some extent problematic, the results of both analyses are discussed separately and in combination.

12.4 Results

A total of 1,269 spontaneous non-nutritive swallows performed during wakefulness were included in the statistical analyses: 712 for neonates, 157 for one-year-olds, 200 young adults and 200 for elderly adults.

12.4.1 Breathing-Swallowing Coordination

12.4.1.1 Neonates Versus One-year-olds

A repeated-measures ANOVA revealed no overall age effect [$F(1, 9) = .483$, $p = .505$] but a respiratory-phase category effect [$F(4, 36) = 10.1$, $p < .001$]. LSD testing revealed that the

[6] Adjustment of infant BSC involved recalculation of the proportional distribution of swallows in II, IE, EE, and EI respiratory-phase categories, thus excluding the 172 P swallows in the database.

proportional distribution of EE swallows was higher than II, EI, and P. The proportional distribution of IE swallows was also higher than P and II. The repeated-measures ANOVA also revealed an interaction of respiratory-phase category and age [$F(4, 36) = 10.2$, $p < .001$]. LSD calculations revealed that the proportional distribution of EI was greater in one-year-olds but P was greater in neonates. Figure 12.1 represents the proportional distribution of swallows in all five respiratory-phase categories for neonates and one-year-olds. The results of analyses reported below (i.e., comparisons to adults) are also represented in Figure 12.1 for ease of reference.

In order to determine the impact of the exclusion of neonatal P swallows (for future comparison to adults) on the comparison to one-year-old BSC (Figure 12.2), the proportional distribution of swallows for neonates was recalculated to exclude P swallows (172 out of the total of 712 swallows). Repeated-measures ANOVA revealed no age effect [$F(1, 9) = .101$, $p = .758$] or interaction of age and respiratory-phase category [$F(3, 27) = 2.21$, $p = .110$] but it did reveal a respiratory-phase category effect [$F(3, 27) = 14.6$, $p < .001$]. LSD calculations revealed that the proportional distribution of EE swallows was higher than II and EI, and IE was greater than II. Figure 12.2 represents the proportional distribution of swallows in all respiratory-phase categories except P, for neonates and one-year-olds. As for Figure 12.1, the results of the comparisons to adults, reported below, are also represented in Figure 12.2 for ease of reference.

12.4.1.2 Neonates Versus Young and Elderly Adults

The first MANOVA of the pattern of neonatal BSC to that of adult groups revealed an age effect for the following respiratory-phase categories: II [$F(2, 27) = 3.99$, $p = .030$], IE [$F(2, 27) = 6.76$, $p = .004$], EE [$F(2, 27) = 7.26$, $p = .003$], and P [$F(2, 27) = 34.0$, $p < .001$]. Pairwise comparisons revealed that neonates differed from both young and elderly adults for IE ($p = .004$ and $p = .003$, respectively), EE ($p = .002$ and $p = .003$, respectively), and P categories ($p < .001$ for both adult age groups). Neonates exhibited higher proportions of IE and P, but lower proportions of EE swallows. Furthermore, neonates exhibited higher proportions of II swallows ($p = .010$) and EI ($p = .028$) than elderly adults (Figure 12.1).

For reasons described above (section 12.3), the proportional distribution of swallows for neonates was recalculated to exclude P swallows (172 out of the total of 712 swallows), and

the MANOVA was performed on the new data. This MANOVA revealed age effects for II [$F(2, 27) = 5.25$, $p = .012$] and IE [$F(2, 27) = 18.5$, $p < .001$] respiratory-phase categories. The neonates exhibited higher proportions of II and IE swallows than the young adults ($p = .024$ and $p < .001$, respectively) and elderly adults ($p = .005$ and $p < .001$, respectively, Figure 12.2).

12.4.1.3 One-year-olds Versus Young and Elderly Adults

By 1 year, infants no longer swallowed during respiratory pauses or performed consecutive swallows, thus the MANOVA comparing one-year-old infants to adult groups compared only II, IE, EE, and EI respiratory-phase categories. This MANOVA revealed an age effect for the following respiratory-phase categories: II [$F(2, 27) = 8.79$, $p = .001$], IE [$F(2, 27) = 12.9$, $p < .001$], and EE [$F(2, 27) = 7$, $p = .004$]. Pairwise comparisons revealed that one-year-olds exhibited higher proportions of II and IE swallows than young adults ($p = .002$ and $p < .001$, respectively) and elderly adults ($p = .001$ and $p < .001$, respectively, Figure 12.2) but lower proportions of EE than young ($p = .003$) and elderly adults ($p = .004$).

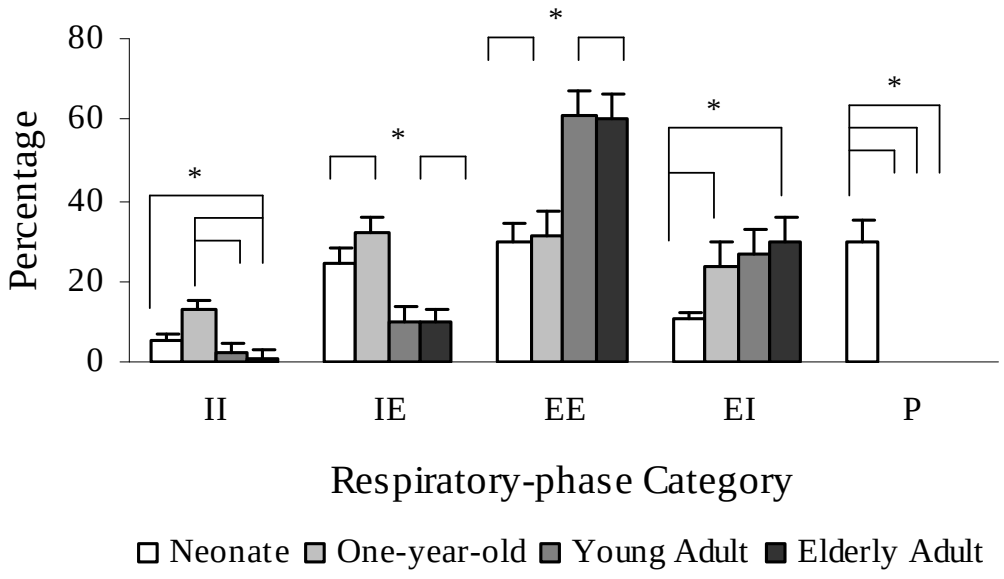


Figure 12.1 Proportional distribution of swallows (means and standard errors) in all five respiratory-phase categories for neonates, one-year-olds, and young and elderly adults.
Note: * = significant difference ($p < .05$) determined by pairwise comparisons.

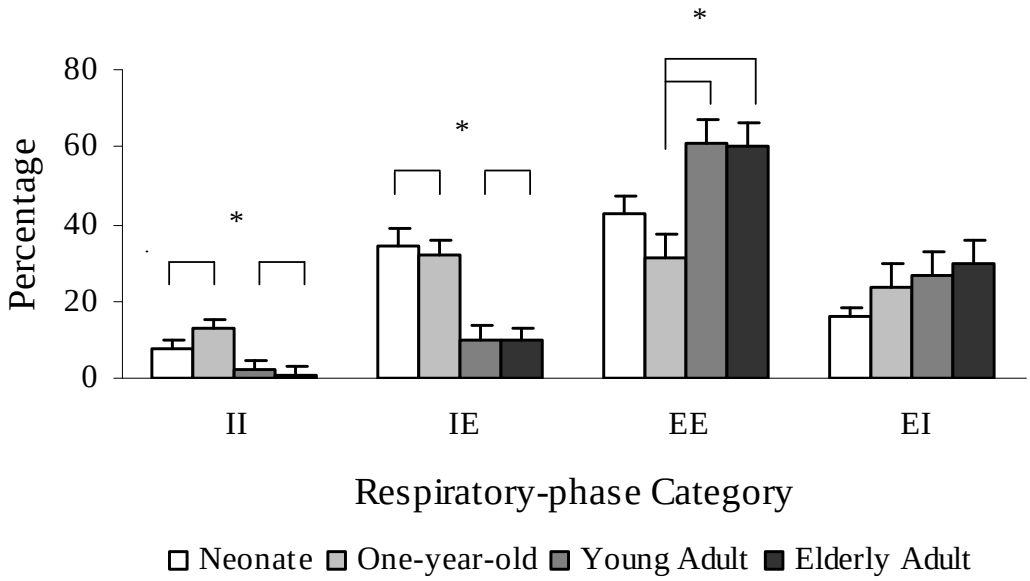


Figure 12.2 Proportional distribution of swallows (means and standard errors) in the four respiratory-phase categories (excluding mid-pause swallows) for neonates, one-year-olds, and young and elderly adults.
Note: * = significant difference ($p < .05$) determined by pairwise comparisons.

12.4.2 Swallowing Apnoea Duration

12.4.2.1 Neonates Versus One-year-olds

The mean SAD for neonates was 709.1 ms (SE ± 31.6 ms) and for one-year-olds it was 742.8 ms (SE ± 67.6 ms). Repeated-measures ANOVA revealed no age effect for SAD [$F(1, 9) = 0.16$, $p = .696$].

12.4.2.2 Neonates Versus Young and Elderly Adults

The mean SAD for neonates was 709.1 ms (SE ± 62.5 ms), for young adults it was 697.3 ms (SE ± 62.5 ms), and for elderly adults it was 907.1 ms (SE ± 62.5 ms). A univariate ANOVA revealed an age effect for SAD [$F(2, 27) = 3.55$, $p = .043$]. Pairwise comparisons showed that SAD of neonates ($p = .034$) and young adults ($p = .025$) were shorter than elderly adults (Figure 12.3).

12.4.2.3 One-year-olds Versus Young and Elderly Adults

The mean SAD for one-year-olds was 742.8 ms (SE ± 71.4 ms), young adults 697.3 ms (SE ± 71.4 ms), and for elderly adults it was 907.1 ms (SE ± 71.4). A univariate ANOVA revealed no age effect for SAD [$F(2, 27) = 2.39$, $p = .111$].

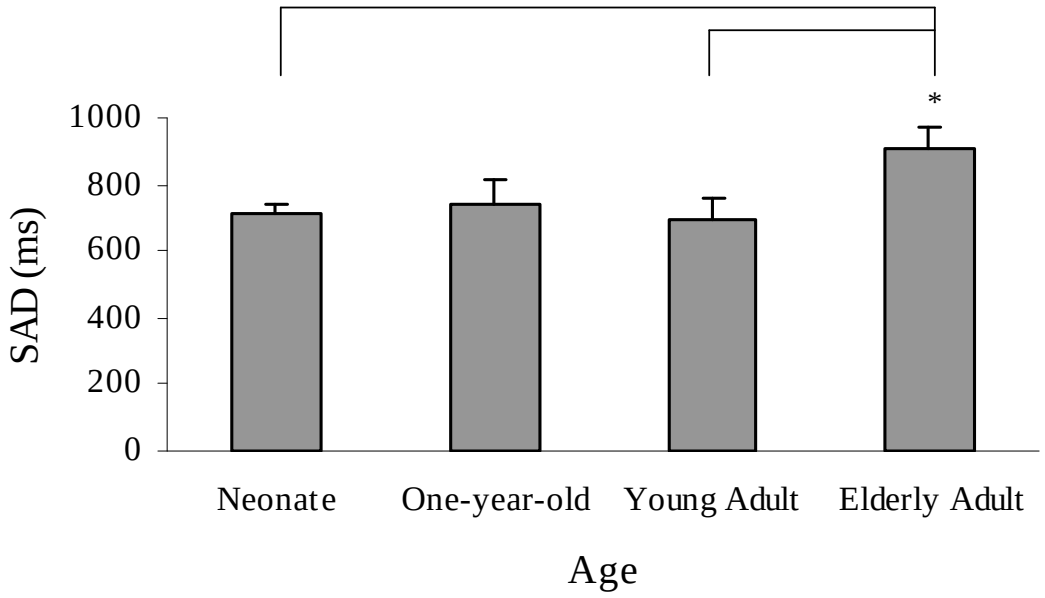


Figure 12.3 The mean duration and standard error scores of SAD for spontaneous swallows performed during wakefulness for neonates, one-year-olds, and young and elderly adults. Note that * indicates the significant difference ($p < .05$) determined by pairwise comparisons between neonates, young adults and elderly adults. Pairwise comparisons between one-year-olds and both adult groups revealed no overall age effect.

12.5 Discussion

The data presented in this chapter describe the maturation of BSC before and after one-year of age. The increase of SAD with advanced age is also presented. Specifically, the BSC of neonates and one-year-old infants differed primarily in terms of P swallow proportions which were present in neonates and absent in one-year-olds. This became apparent when comparing five (II, IE, EE, EI, and P) then four (no P) respiratory-phase categories, the former comparison yielding a difference in IE and P swallow proportions and the latter yielding no respiratory-phase category differences between the two infant age groups. Thus, early maturation of BSC during infancy may be attributed to a decline in P swallow proportions. In general, the BSC of both the neonates and the one-year-olds differed from both young and

elderly adult groups, suggesting that non-nutritive spontaneous BSC during wakefulness matures beyond the first year of life.

The distinguishing feature of the early maturation of BSC was characterized by a decline in P swallow proportions. As discussed previously (sections 5.5. and 6.5), this may reflect the increasing fusion of continuous respiration with swallowing as a result of the maturation of the interaction of respiratory and swallowing CPGs. The decline of P swallow proportions may also be a sign of the declining frequency of respiratory pauses with age.

The comparisons between neonatal and adult BSC (both with and without P swallow proportions) indicated that neonatal and adult BSC differ. Although the number of respiratory-phase categories subject to an age effect was higher for the comparison that included P swallow proportions than the comparison that excluded P swallows, both comparisons revealed higher neonatal II and IE swallow proportions compared to one or both adult groups. Similarly, II and IE swallow proportions of one-year-olds were higher than both adult groups. Thus, the overall pattern maturation of non-nutritive BSC between birth and adulthood can be attributed primarily to decreases in II, IE, and P swallow proportions.

The results of Chapter 5 and 10 identify that feeding throughout the first year of life and volitional swallowing control in adults, respectively, are key factors influencing BSC. In combination, these results suggest that volition and attention, and therefore cortical influences, are major determiners of BSC. Thus, the less pronounced and protracted maturation of non-nutritive BSC in the present chapter could perhaps reflect cortical maturation.

BSC of young and elderly adults did not differ in the present study which is in contrast to the finding that suggests that BSC is altered by advanced age: elderly are more likely to inspire prior to swallowing than young adults (Shaker et al., 1992). This discrepancy may be due to the categorization of swallows into six respiratory-phase categories (Shaker et al., 1992) instead of four in the present study, making it difficult to directly compare the results of these two studies. Advanced age, however, did influence SAD in the present study. Although there was no maturation in the first year of life, the SAD of neonates and young adults was shorter than that of elderly adults. This is consistent with prior research indicating an increase in SAD with advanced age in females (Hiss et al., 2001) and in adults over 50 years (Miyazaki et al., 1994). It is also consistent with the elderly-associated increases in other swallowing duration

measurements such as pharyngeal pressure (Martin-Harris et al., 2005; Perlman et al., 1993; Rademaker, Pauloski, Colangelo, & Logemann, 1998; Robbins et al., 1992). Given that the maturational patterns of SAD differ to that of BSC, this again supports the notion that the neural controls for SAD are relatively independent (Hiss et al., 2003).

The effect of advanced age on SAD may reflect age-related brainstem changes and is supported by research in preterm infants. Within a few weeks the SAD of preterm infants decreases to approximate that of term controls once they reached term age (Hanlon et al., 1997). This rapid maturation pattern is more likely due to brainstem maturation than cortical, given the relatively protracted maturation of the human cortex (Gibson, 1991). Similarly, the results from the preceding two chapters (10 and 11) suggest that SAD is more likely brainstem governed. Thus, the effect of advanced age may be due to brainstem neural loss that is associated with the normal ageing process (Alvarez et al., 2000; Ransmayr et al., 2000; Tang et al., 2001-2002).

12.6 Conclusions

Non-nutritive BSC and SAD exhibit different maturation patterns which suggests differing neural control mechanisms for these two phenomena. These results, paired with those from preceding chapters suggest that the maturation of higher CNS structures is more likely reflected in the difference between infant and adult BSC, and age-related brainstem changes account for the changes in SAD with advanced age.

Chapter 13. Concluding Remarks

13.1 Breathing-Swallowing Coordination

The key role of the brainstem in the coordination of breathing and swallowing is apparent in the results of this research. First, the similarities between infant and adult BSC, specifically the predominant incidence of neonatal post-swallow expiration (IE and EE respiratory-phase categories), persists into adulthood. This persistence of a neonatal phenomenon suggests brainstem influence. This argument is based upon the patterns of neural development. The brainstem is relatively developed at birth compared to higher CNS structures (Gibson, 1991). Second, the early but declining impact of feeding on infant BSC (Chapter 5) may be partially due to brainstem maturation given the results of prior research that indicate that postnatal brainstem maturation may be associated with early maturation of features of respiration and/or feeding (Denavit-Saubie et al., 1997; Dutschmann et al., 2004; Henderson-Smart et al., 1983; Sumi, 1975; Thexton & Griffiths, 1979).

On the other hand, cortical modulation of BSC appears more subtle and limited to conditions in which attention is brought to volitionally-initiated swallowing in both infants (nutritive swallows) and adults (non-nutritive swallows). This is evident by the absent effect of reduced level of arousal on the BSC of infants (Hypotheses 4 and 5 rejected) and adults (Hypothesis 9 rejected) and the absent effect of arousal from NREM sleep in young adults (Hypothesis 11 rejected). The combination of these results suggests that the increase in global cortical activity associated with wakefulness and arousal is insufficient to alter BSC even in cortically mature young adults. Only when volitional control over swallowing was introduced was BSC altered. This is illustrated by the more pronounced maturation of nutritive BSC (Chapters 4 and 5) than non-nutritive BSC (Chapters 6 and 12) in the first year of life. Although feeding swallows are not necessarily voluntary in infants, it is the condition closest to volitional swallowing that can be behaviourally elicited. Also, the age at which the large majority of swallows were followed by expiration coincided with normal developmental milestones associated with the cortex: reflex suppression (Sarnat, 1989) and increasing voluntary control over feeding (Stevenson & Allaire, 1991). By 1 year of age, nutritive BSC was largely adult-like (Hypothesis 1 accepted). In adults, volitional cortical modulation was also apparent (Hypothesis 10 accepted): volitional swallowing influenced BSC compared to spontaneous

wake swallows where participants were vigilant, but their attention was directed towards the completion of a distraction task and not swallowing.

Although not specifically evaluated in this research, the exact cortical sites involved in the mediation of BSC during volitional swallowing are likely to be those involved specifically in volitional planning of swallowing: the supplementary motor cortex (Huckabee et al., 2003), cingulate cortex (Wantanbe et al., 2004), insular cortex (Dziewas et al., 2003; Wantanbe et al., 2004), and frontal operculum (Dziewas et al., 2003). This list of sites can be further refined to include those cortical sites involved in *both* swallowing and respiration: insular cortex (Davenport & Reep, 1995; Kern, Jaradeh et al., 2001), premotor cortex (Colebatch et al., 1991; Mosier & Bereznaya, 2001), motor cortex (Colebatch et al., 1991; Martin et al., 2001), and supplementary motor cortex (Colebatch et al., 1991; Mosier & Bereznaya, 2001). Further refinement to include potential sites inferred from the patterns of postnatal neural development, such as the frontal lobes, may also be necessary.

In Chapter 12, it was shown that non-nutritive BSC matures during infancy and up to adulthood (Hypothesis 12 accepted). Processes within the cortex, like synaptogenesis, occur within the first 2 years of life and cortical myelination and dendritic arborization occur earlier in primary motor and sensory regions (Huttenlocher & Dabholkar, 1997). During infancy there is an increase in synaptic density and cortical and white matter volume, the latter continuing into the fourth or fifth decade of life (review by Sowell et al., 2004). In general, these maturation processes are more obvious in the frontal lobes (review by Sowell et al., 2004). Thus, age-related maturation of the frontal lobes may be reflected in the maturation of BSC between infancy and adulthood. Since the BSC of young and elderly adults did not differ for volitional (Chapter 9) or non-volitional swallows (Chapter 12) deterioration of the CNS (Alvarez et al., 2000; Andersen et al., 2003; Ransmayr et al., 2000; Tang et al., 2001-2002) including the cerebral cortex (Resnick et al., 2003; Simic et al., 2005; review by Sowell et al., 2004) associated with normal ageing appears insufficient to alter BSC.

Cortical sites involved in volitional swallowing and respiration, and which show considerable postnatal development, such as frontal lobes, may be the cortical sites involved in BSC. By deduction, these include the insular cortex and the SMA. In support of the former, previous research has found overlapping gastromotor and respiratory areas in the rat insular cortex (Aleksandrov et al., 2000) and a link between the insular cortex, attention disorders, and gastrointestinal problems (Binstock, 2001). There is less support for SMA involvement in

BSC. The SMA is generally involved in the organisation of intricate temporal motor sequences (Gerloff, Corwell, Chen, Hallett, & Cohen, 1997; Tanji & Shima, 1996). The SMA is also activated by volitional inspiration and expiration (Evans et al., 1999) and volitional swallowing (Satow et al., 2004), thereby indicating that the SMA is possibly involved in respiratory-phase motor planning, and could be involved in its integration with volitional swallowing.

Whether the SMA and insular cortex influence brainstem CPGs via direct or indirect pathways is difficult to surmise; however, both indirect and direct corticobulbar pathways are associated with respiration (Davenport & Reep, 1995) and swallowing (review by Jean, 2001). Indirect BSC-related pathways may involve those subcortical sites that have been identified as being active in both respiration and swallowing: the basal ganglia (Fink et al., 1996; Mosier & Bereznaya, 2001) and thalamus (Davenport & Reep, 1995; Mosier & Bereznaya, 2001).

But does the cortex purely modulate efferent output, or process afferent information which modulates motor output? Although the present research cannot make this distinction, the results interpreted in the light of prior research, support primarily efferent cortical modulation with relatively limited involvement in afferent processing.

Although the brainstem is undoubtedly involved in afferent processing, as evidenced by the elicitation of reflexes following oral stimulation in decerebrate animals (Thexton, 1973), cortical processing of swallowing and respiratory information is well documented. For example, the cortex plays a role in afferent processing during the pharyngeal stage of swallowing (Hiraoka, 2004) and the activity of neurones in the animal cortex are influenced by afferent stimulation during swallowing (Jean, 2001). Furthermore, afferent swallowing information is transmitted to the cortex from pontine structures (Car, Jean, & Roman, 1975; Jean, Car, & Roman, 1975; Sumi, 1972). Similarly, respiratory-related afferent information is conveyed to the cortex (Davenport & Reep, 1995) via projections of the phrenic nerve fibres in animals (Davenport, Thompson, Reep, & Freed, 1985). The existence of cortical afferent and efferent processing for swallowing and respiration suggests that it is conceivable that there is cortical afferent processing that can influence BSC. BSC is sensitive to afferent information in that infant BSC was altered dramatically by feeding (Hypothesis 2 accepted) in the first few months of life and is also altered by the size of the ingested bolus in adults (Preiksaitis et al., 1992). Furthermore, the impact of feeding on BSC declined with postnatal

age (Hypothesis 3 accepted), a time when maturing cortical input is most likely to increase. This implies that the cortex participates in the afferent and efferent modulation of BSC that, with maturation, minimizes the effect of feeding on BSC to approximate the absent effect on BSC in adults (Nishino et al., 1985). Electrocortical activity of neonates is altered during feeding, but not necessarily during non-nutritive sucking, thus indicating that oral stimulation alone is inadequate to result in cortical activation (Lehtonen et al., 1998). Feeding also involves heightened attention, suggesting that feeding-related electrocortical changes observed in infants are, in part, modulated by the neural mechanisms involved in hunger and satiety, as well as those involved in attention and alertness, such as the hypothalamus, limbic system, and brainstem (Lehtonen et al., 1998). In terms of BSC neural modulation, the present study supports the activation of these structures as well but, given the absent effect of altered level of arousal on BSC of individuals at all ages (Hypotheses 4, 5, and 9 rejected), the emphasis rests with those structures involved in attention and volitional control rather than satiety and alertness.

The volitional element of cortical control of BSC in the absence of afferent stimulation further suggests that the cortex is involved in the planning and execution of the pattern of BSC. This is observed for swallowing. The cortex may be more heavily involved in the planning (Huckabee et al., 2003) and execution (Jean & Car, 1979; Miller, 1999) of volitional swallowing than sensory processing. This argument is not novel. Cortical potentials for tongue protrusion and nutritive swallowing are similar despite the obvious difference in afferent stimulation between the two conditions (Satow et al., 2004). Moreover, the ‘cortical swallowing area’ is most likely purely involved in the initiation of swallowing, with no further influence on motor output sequencing (Jean & Car, 1979). This is supported by the fact that many animal cortical sites elicit swallowing when stimulated electrically: anterolateral frontal cortex, frontal operculum, orbitofrontal cortex, lateral pericentral cortex, and insular cortex (review by Miller, 1999).

The pathways and mechanisms by which the cortex exerts influence on BSC also remain speculative. Cortical suppression of respiratory activity has been suggested (Hadjikoutis et al., 2000; Neubauer, 1990). Specifically, Hadjikoutis et al. (2000) hypothesized that damage to the corticobulbar tract results in reduced suppression of inspiration, evident by the propensity for an increase in post-swallow inspiration in patients with damage to this area. This is also reflected in the results of the present study. There was a rise in the proportion of a post-swallow expiration category (IE) and a fall in a post-swallow inspiration category (EI) during

volitional swallowing in adults. Thus, during volitional swallowing the cortex may directly or indirectly inhibit respiratory brainstem CPGs to increase the incidence of post-swallow expiration via the pathways described above. During volitional swallowing, BSC did not alter with a change in body position in adults (Hypothesis 8 rejected). However, as detailed in Chapter 9, caution must be exercised in interpreting $p = .063$ as strictly non-significant. Thus, these results tentatively suggest that BSC is insensitive to peripheral neural feedback associated with body position. In the light of the purported cortical inhibition of respiratory brainstem CPGs discussed above, these results may reflect cortical overriding of any position-related influences on CPGs. Clarification of this would involve the comparison of non-volitional swallows performed in the same four body positions.

Finally, although little is known about the role of the cerebellum in swallowing, its potential role in BSC is not entirely unlikely. The cerebellum is involved in volitional swallowing (Mosier & Bereznaya, 2001; Zald & Pardo, 1999) and breathing (McKay, Evans, Frackowiak, & Corfield, 2003). According to Aumann (2002), cerebellar modulation of volitional motor activity occurs largely via a pathway involving the thalamus and primary motor cortex. Thus, the cerebellum may have contributed to the impact of volitional swallowing on adult BSC (Chapter 10). Similarly, postnatal development of the cerebellum may have contributed to the maturation of nutritive infant BSC in the first year of life (Chapter 4) since cerebellar maturation continues throughout the first year of life (Dobbing & Sands, 1973) and a recent review concluded that cerebellar maturation is mirrored by motor coordination in animals (review by Swinny, van der Want, & Gramsbergen, 2005). Finally, the cerebellar role in integrating sensory input and motor output (review by Apps & Garwicz, 2005), timing, and motor coordination (Shannon et al., 2004), or the adaptation of motor coordination (review by Thach et al., 1992) suggests that it may also be involved in the maturing impact of feeding on BSC (Chapter 5).

In conclusion, the results of this research indicate that although the brainstem is crucial in governing BSC throughout the human lifespan, BSC may become increasingly amenable to descending cortical influences (and possibly cerebellar modulation) with postnatal maturation, but specifically those cortical sites involved in volition and attention. Although speculative, prior swallowing, respiratory, and motor control research suggests that these sites are found in the frontal lobe and may be limited to the insular cortex and SMA.

13.2 Swallowing Apnoea Duration and Peak Submental Surface Electromyogram

SAD was influenced by feeding in infants (Chapter 7), body position and gender in adults (Chapter 9), and advanced age (Chapter 12). For reasons outlined in the relevant chapters, but particularly the combination of all these results, SAD is most likely nearly entirely brainstem mediated. First, the impact of feeding on infant SAD was stable throughout the first year of life (Hypothesis 6 accepted). In addition, nutritive and non-nutritive SAD did not change in the first year of life (Hypothesis 7 accepted), nor was it different to that of young adults (Chapter 12). This is despite the marked supramedullary maturation that occurs during infancy and, therefore, implicates principal brainstem control. Second, only advanced age resulted in an increase in SAD. This may be partially due to brainstem neural loss associated with the normal ageing process (Alvarez et al., 2000; Ransmayr et al., 2000; Tang et al., 2001-2002), although age-related neural loss is not isolated to the brainstem (Resnick et al., 2003). Third, SAD was not altered by level of arousal. Given the dramatic increases in cortical activation associated with increasing arousal (review by Muzur et al., 2002) and that SAD is impervious to the fluctuations in the degree of cortical activity, primary brainstem control over SAD is therefore implied. The combination of the above findings suggests that the primary site controlling SAD is the brainstem.

This research contributes to the argument that “SA is a central event with its occurrence receiving a dedicated neural command” (Hiss et al., 2003, p. 297). It seems that the duration of SA may be controlled by neural networks that are partially independent of those controlling respiration, swallowing, and BSC. First, adult SAD was not subject to the same influences that altered BSC which are likely to be cortically controlled (i.e., early maturation and volitional swallowing). Thus, the neural controls of SAD must be somewhat independent of those involved in BSC. Second, the maturation patterns of SAD do not mirror those of respiration and swallowing, which would be expected if the swallowing and respiratory neural pools were largely shared with SAD. However, SAD appears to be prone to the gravitational forces that act upon hyolaryngeal excursion. This may represent the interaction or the overlap of swallowing and SAD neural pools or simply the effect of gravity on swallowing biomechanics.

Peak submental SEMG increased notably during volitional swallowing and minimally for males than females in most body positions. Higher submental SEMG values in males may

reflect increased muscle recruitment required to achieve adequate hyoid movement due to their more inferior hyoid resting position (Ishida et al., 2002).

13.3 Clinical Applications

The findings of the present studies have implications for the patient population with cortical damage. In particular, these results suggest that infants and adults with cortical damage, and subsequent diminished volitional control over swallowing, may exhibit aberrant patterns of BSC. Although a direct link between aberrant BSC patterns and adverse outcomes has yet to be established, the literature indicates a high likelihood that aberrant BSC is associated with (McPherson et al., 1992) but may not be the cause of aspiration (Hadjikoutis et al., 2000). Since the incidence of silent aspiration may be as high as 52% of all aspirating patients across a variety of disorders (Garon, Engle, & Ormiston, 1996) and routine videoflouroscopic evaluations on all patients with CNS damage is impractical, additional non-invasive indicators of aspiration risk, such as aberrant BSC, would be clinically useful.

It is possible that the elderly are particularly susceptible to the adverse effects of cortical damage, which may be a clinically important consideration in the bed-side evaluation. This is supported by the reported age-related changes in motor processing, with greater bilateral recruitment of primary sensorimotor and premotor cortices (Sailer et al., 2000) and reduced cortical inhibition in healthy elders (Peinemann et al., 2001). Similarly, there is a decline in cognitive inhibition of information processing necessary to achieve focussed attention (Milham et al., 2002). Thus, in the event of cortical damage, the elderly may be more prone to aberrant patterns of BSC during volitional swallowing than younger adults with the same lesion.

Hence, results from the current studies provide normative data that will be of value in the identification of pathologic BSC and SAD in both the paediatric and adult patient populations. It is acknowledged that the small sample size limits its applicability to the general population but normative data for older infants, in particular, is otherwise not available. Feeding difficulties exhibited by preterm infants are thought to be most likely indicative of neuromuscular immaturity (Bu'Lock et al., 1990), thus deviations from these normative BSC and SAD patterns may also prove to be an indication of neuromuscular immaturity or damage. For example, despite the lack of evidence associating abnormal SAD with adverse outcomes,

Hanlon et al. (1997) concluded that SAD is determined by neural maturation in preterm infants. Thus, deviation from the norms provided by the present research may be considered a mark of neurological immaturity in infants. Given that the results of the present study support primarily brainstem-mediation of SAD, abnormal SAD may be an important indicator of a brainstem lesion.

Finally, as discussed in section 2.4.3.1 and throughout Chapter 5, there may be a link between BSC and SIDS. This speculation is supported by the occurrence of breathing abnormalities such as a higher incidence of apnoea during feeding or sleep in future SIDS victims (Steinschneider et al., 1982) and the likelihood that oropharyngeal stimulation of the LCR (which includes swallowing) results in the prolongation of apnoea (Thach, 1997) and possibly even sudden infant death (Thach, 2000). Furthermore, Sumi (1975) purported a causal link between oropharyngeal stimulation and general impaired functioning of the immature medulla under certain circumstances such as sleep. Alternatively, it may be delayed or abnormal development of suprabulbar or cerebellar structures that impair BSC and subsequently result in SIDS; patterns of hypomyelination, particularly in pyramidal, cerebellar, and pre-frontal-temporal-limbic pathways, in SIDS victims suggest that the central control of somatomotor and visceromotor systems for cardiorespiratory control may be impaired (Kinney et al., 1991). BSC of feeding differs from that of non-nutritive wake swallows particularly between 2 weeks and 2 months of age (Chapter 5). This suggests that BSC is most susceptible to oropharyngeal stimulation during a period in which the incidence of SIDS is high (Malloy & Freeman, 2004). It is recognized, however, that this merely offers support for a speculative link between BSC and SIDS, and that further research is required before conclusions can be drawn.

13.4 Strengths and Critique of Present Research

There are two key methodological strengths of the present research. The first is the comprehensive and longitudinal nature of the assessment of BSC and SAD in infants from soon after birth to 1 year of age. Although the number of participants and, in some cases, the sample size was small, similar data appear not to have been previously reported. The infant data, in particular, may prove to be a valuable database from which comparisons to patient populations can be made. Since much of the available BSC and SAD data is obtained from preterm infants (Koenig et al., 1990; Lau et al., 2003; Menon et al., 1984; Mizuno & Ueda,

2003; Wilson et al., 1981), a population that differs neurologically from term infants with regard to swallowing (Jeffery et al., 2000) and cardio-respiratory functions (Miller, Carlo, DiFiore, & Martin, 1988), preterm infant data cannot be considered normative.

The second key strength of this research is that BSC was monitored in a truly reflexive, natural swallowing condition, during sleep. This, too, has never been carried out before in adult humans without the use of anaesthesia and with EEG confirmation of sleep status.

However, even during NREM sleep, the cerebral cortex is not entirely inactive (Hofle et al., 1997), thus cortical and brainstem influences may have been present in both conditions, thereby explaining the absent effect of sleep on BSC and SAD. Previously, authors have argued that although the cortex is unlikely to initiate reflexive swallows, however there may still be brainstem interaction with suprabulbar and cortical structures during NREM sleep (review by Ertekin & Aydogdu, 2003). Unfortunately, there is no ethical way in which complete cortical quiescence can be induced; hence sleep remains the condition that most closely approaches cortical quiescence in live healthy humans.

The present research is also limited in the inferences that can be made regarding the neural substrates of BSC in both infants and adults given that the methodological design is behavioural in nature. Formal investigation of myelination and cortical development of the infant participants using neuroimaging techniques would have indicated which neural developmental processes coincided with advances in BSC maturation. This would implicate the processes and structures involved in the maturation of BSC and, therefore, the control of BSC and SAD. Additionally, more detailed assessment of respiratory patterns such as rate, variability, and tidal volume, would have indicated the extent to which respiratory maturation accounted for the maturation of BSC, particularly with reference to the incidence of respiratory pauses.

13.5 Future Research

It was shown that BSC during non-nutritive wake swallows is not mature by 1 year of age (Chapter 12), thus future longitudinal research is required to determine the age of non-nutritive BSC maturation. Furthermore, a sample size greater than that of the present research would strengthen the findings of the infant (Part II) and adult (Part III) studies. With specific

reference to Chapter 9, the inclusion of a greater number of adult participants or a greater number of swallows performed by these participants should provide a more definitive resolution to the still questionable effect of body position on BSC and peak submental SEMG.

Further investigation of the influence of cortical activity on the BSC of patients in a deep coma or that of cortically dead patients would contribute to the understanding of global cortical modulation of BSC. Furthermore, investigation of the BSC of patients with discrete lesions (e.g., ischemic infarcts) in any of the areas known to be involved in swallowing and breathing, including the primary and premotor cortices, the SMA, insular cortex, basal ganglia, thalamus, prefrontal lobes, and cerebellum may identify those sites involved in BSC. The SMA and insular cortex are of particular interest given their suspected role in BSC (discussed above in section 13.1). Although the effect of a discrete lesion to the insular cortex on some aspects of adult human swallowing has been studied (Daniels & Foundas, 1997), the effect on BSC remains unknown. Investigation of BSC with a combination of neuroimaging and mapping techniques, such as simultaneous fMRI and high resolution EEG may provide the temporal and spatial resolution necessary to elucidate not only those sites involved in BSC but the nature of their contribution (e.g., planning, execution, modulation).

One of the key clinical questions that remains unsolved is the link between deviant BSC, in particular a high incidence of post-swallow inspiration, and aspiration. Some authors argue that post-swallow inspiration may be result in aspiration (McPherson et al., 1992) while, others argue that it is merely indicative of respiratory or swallow pathology (Hadjikoutis et al., 2000). Although the importance of adequate respiratory-swallow integration in adults and infants has been established (Hadjikoutis et al., 2000; McPherson et al., 1992; Miller & Kiatchoosakun, 2004; Morton et al., 2002; Nilsson et al., 1997; Pinnington, Smith et al., 2000), further investigations into BSC are likely to prove of value.

Another important clinical question that should be addressed is whether cortical damage can result in impaired upper oesophageal sphincter function. The results of Chapter 10 suggest that the cortex can influence submental muscle activity which is representative of hyolaryngeal excursion. Hyolaryngeal excursion plays a major role in the opening of the upper oesophageal sphincter (Cook, Dodds, Dantas, Massey et al., 1989), in particular, the anterior hyoid movement (Ishida et al., 2002). Thus, patients with cortical damage may present with dysphagia characterized by impaired UOS opening.

Compared to adults, there are many normative swallowing-related phenomena in infants that require investigation. Knowledge of the biomechanics of swallowing and its integration with respiration in human infants is inadequate and limited to descriptions of observations (Ardran et al., 1958; Weber et al., 1986). Of particular interest is the description of continued respiratory efforts during swallowing, determined by plethsmography, by Wilson et al. (1981). Unfortunately, these data were obtained from premature infants who were not all healthy. Thus, whether healthy term infants continue respiratory efforts during swallowing remains unknown and future research needs to confirm the central component of SA in infants as it has for adults (Hiss et al., 2003; Martin et al., 1994; Nishino & Hiraga, 1991; Preiksaitis & Mills, 1996; Smith et al., 1989). Furthermore, the present research indicates that there is further maturation of non-nutritive BSC between infancy and adulthood. Investigation in children older than 1 year is necessary to determine precisely when non-nutritive BSC matures.

Finally, the results of this research indicate that a brainstem-generated BSC pattern can be altered by supramedullary structures. In accordance with this suggestion, Narita et al. (1999) found changes to the temporal sequencing of swallow-associated EMG activity in primates as a result of the temporary deactivation of lateral pericentral cerebral cortex. Hence, they suggest that muscle programming may not be solely dependent on brainstem CPGs. Future research should aim to determine whether other features of swallowing and/or respiratory coordination are not purely brainstem-driven.

APPENDICES AND REFERENCES

Appendices

Appendix A. Summary of Key Nerves Involved in Afferent and Efferent Swallowing Innervation

Afferent nerves involved in swallowing

Note: The NTS consists of the nuclei of cranial nerves VII, IX, and X.

Sensory Function	Innervation
General sensation, anterior two-thirds of tongue	Lingual nerve, trigeminal (V)
Taste, anterior two thirds of tongue	Chorda tympani, facial (VII)
Taste and general sensation, posterior one-third of the tongue	Glossopharyngeal (IX)
Mucosa of the valleculae	Internal branch of the SLN (vagus, X)
Primary afferent	Glossopharyngeal (IX)
Secondary afferent	Pharyngeal branch of the vagus (X)
Tonsils, pharynx, soft palate	Glossopharyngeal (IX)
Pharynx, larynx, viscera	Vagus (X)

Efferent nerves involved in swallowing

Note: The nucleus ambiguus consists of the nuclei of cranial nerves IX and X.

Efferent/Stage	Innervation
Oral	
Masticatory, buccinator, floor of mouth	Trigeminal (V)
Lip sphincter	Facial (VII)
Tongue	Hypoglossal (XII)
Pharyngeal	
Constrictors and stylopharyngeus	Glossopharyngeal (IX)
Palate, pharynx, larynx	Vagus (X)
Tongue	Hypoglossal (XII)
Oesophageal	
Oesophagus	Vagus (X)

Adapted from Morrell, R. M. (1984). The neurology of swallowing. In M. E. Groher (Ed.), Dysphagia: Diagnosis and Management. Boston: Butterworths.

Appendix B. Prior Breathing-Swallowing Coordination Research

Percentage Swallow Apnoeas Occurring Before, During, and After Expiration in Healthy Adult Humans

The missing cells reflect the differing methods of statistical analysis and reporting of data (section 2.4.3.2).

Study	Bolus	Method of bolus administration	Before expiration	During expiration	After expiration
Hirst, Ford, Gibson, & Wilson (2002)	5 ml	Syringe	91.0		
	20 ml	Syringe		Not reported	
	100 ml	Cup	78.5		
	Thin liquid	Straw	63.5		
Hiss, Treole, & Stuart (2001)	10, 15, 20, and 25 ml liquid	Self-administered cup and straw TOTAL	86.0	62.0	75.0
	5 ml	Cup	91.0		
	Thin liquid	Cup	78.5		
	Thin liquid	Straw	63.0		
Kelly, Huckabee, & Friend (in press)	15 ml	Self-administered cup	94.5	78.5	81.8
	Saliva (during sleep)	N/A	84.6	70.8	84.3
Klahn & Perlman (1999)	Liquid and apple sauce	Suspended spoon	100.0	93.0	57 - 86.0
Martin, Logemann, Shaker, & Dodds (1994)	3, 10, 20 ml	Syringed by researcher	100.0	94 - 100.0	93.0
	Thin liquid	Sequential straw drinking	< 100.0		
McFarland & Lund (1995)	Solid bolus	Administered by researcher		> 89.0	
Nishino, Yonezawa, & Honda (1985)	Saliva	N/A		~ 80.0	
	Water bolus	Syringe		~ 80.0	

Appendix B continued…

Study	Bolus	Method of bolus administration	Before expiration	During expiration	After expiration
Nishino & Hiraga (1991)	Saliva (while under anaesthesia)	N/A		Not reported	
Perlman, Ettema, & Barkmeier (2000)	5 and 10 ml	Syringe	96.0		79.0
Preiksaitis, Mayrand, Robins, & Diamant (1992)	Saliva – 20 ml	Self-administered cup	89.2	71.4	81.5
	Saliva	N/A	78.6	67.5	87.3
	5	Self-administered cup	96.3	72.7	76.3
	10	Self-administered cup	100.0	78.2	78.2
	20	Self-administered cup	96.1	72.6	76.5
Preiksaitis & Mills (1996)	5 - 20 ml	Self-administered syringe and cup TOTAL		77.0	
	5 ml	Syringe	92.5		82.5
	10 ml	Syringe	97.5		80.0
	20 ml	Syringe	97.5		62.5
	5 ml	Cup	100.0		80.0
	10 ml	Cup	100.0		72.5
	20 ml	Cup	95.0		51.7
	200 ml	Cup	76.2		
	200 ml	Straw		Not reported	
	Thin liquid	Cup	95.0		85.0
	Thick liquid	Not specified	95.0		75.0
	Syrup	Not specified	100.0		80.0
	Semi-solid	Not specified	95.0		85.0
	Cookie	Not specified	85.0		85.0
	Sandwich meal	Not specified	83.7		

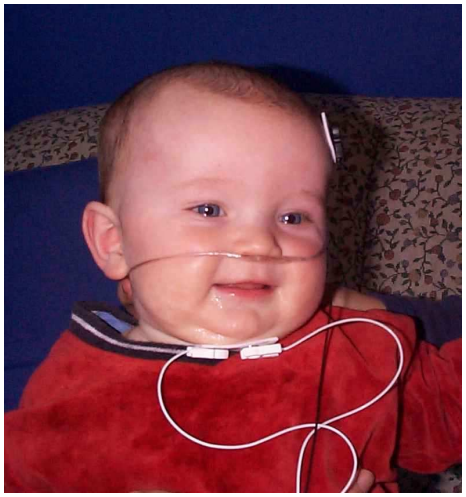
Appendix B continued…

Study	Bolus	Method of bolus administration	Before expiration	During expiration	After expiration
Selley, Flack, Ellis, & Brooks (1989)	5 ml liquid	Administered by researcher	95.0		
Shaker, Li, Ren, Townsend, Dodds, Martin, et al. (1992)	5 ml liquid	Syringed by researcher		Not reported	
	Saliva	N/A	55.0		

Appendix C. Infant Participant Recruitment Poster

Are you pregnant?
Are you going to give birth soon?

We are searching for newborns to participate in non-invasive research looking at swallowing and breathing patterns



Please contact Lauren Ragg or Bronwen Kelly
On 03 364 2987 ext 7161 or ext 7337
Or email lar32@student.canterbury.ac.nz
bmk21@student.canterbury.ac.nz

This research project has been reviewed and approved by the Canterbury Ethics Committee

Canterbury DHB
District Health Board
Te Poari Hauora ō Waitaha

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Appendix D. Infant Participant Information Sheet and Consent Form

You and your child are invited to participate in a research project that investigates the role of the brain and brain development in the coordination of breathing and swallowing in children from birth to the age of seven years.

The project aims to determine whether the coordination of breathing and swallowing differs between sleep and wake in children from birth to the age of seven years.

Your participation will vary between approximately two to six hours when your child is twenty-four hours old, forty-eight hours, one, two and three weeks old, one, two, three, six, nine, twelve and eighteen months, three, four, five, six and seven years of age.

We will ask you **questions** that will provide us with information about your child's health and indicate possible exclusion criteria. The questions will include information pertaining to your family's medical history, your pregnancy and your health during the current and previous (if applicable) pregnancies, your labour and delivery.

Once your child is born you will be asked to answer some questions about your child's development and their feeding each time you visit us. You will be asked to bring your child's plunket book so that their growth can be recorded. Each time we see your child we will perform a brief **non-invasive assessment of your child's reflexes** and **complete a developmental scale** (the Denver II), following which **breathing and swallowing will be monitored** while s/he feeds by the method of your choice, lie on his/her backs while interacting with you, and then while asleep in the same position.

Your child's swallowing will be measured by two pieces of equipment that will be connected to the Kay Elemetrics Swallowing Workstation. The first piece of equipment is called surface electromyography and consists of three electrodes, two of which will be placed under your child's chin. The third will be placed behind his/her ear. This device records muscle activity under his/her chin when s/he swallows. The second piece of equipment is called a laryngeal microphone, which records the sounds generated by your child's swallow. The laryngeal

microphone will be secured on your child's neck with standard surgical tape. Your child's breathing will be measured with a nasal cannula, similar to those used in hospitals to provide patients with oxygen. It is a flexible plastic tube, which has two prongs that rest at the entrance of the nose. Finally, a mercury position switch monitor may be used. This device consists of a small box that is placed around your child's chest and held in position by a soft elastic strap.

Participation is voluntary and you have the right to withdraw from the project at any time, including withdrawal of any information that you have provided.

There are no foreseeable risks in the performance of the tasks and application of the procedures in this study. There is no pain associated with this procedure, however your child may experience some discomfort associated with the unfamiliarity of the equipment and redness of the skin, associated with use of adhesive electrode patches.

Your and your child's right to privacy will be retained. Neither you nor your child's name will appear on the recorded data or on any published material resulting from this research project. Only those directly involved in the research project will have access too your recorded data. Any written data will remain in a locked cabinet in The Swallowing Research Laboratory.

This research assignment is a requirement for the Masters and Doctor of Philosophy Degrees in Speech and Language Therapy. If you have any concerns regarding your participation or would like further information please contact the project supervisor, Maggie-Lee Huckabee, PhD, on (03) 366 7001 extension 7085

This research project has been approved by the University of Canterbury Human Ethics Committee.

Infant Consent Form

I, _____ give consent for _____ to participate in this research project that investigates the coordination of breathing and swallowing in children from birth to seven years of age conducted by Lauren Ragg, Bronwen Kelly and Dr Maggie Lee Huckabee, the Department of Speech and Language Therapy, University of Canterbury, with co-supervision of Associate Professor Richard Jones, of the Canterbury District Health Board, Christchurch School of Medicine and Health Sciences, and University of Canterbury.

I have read and understood the attached information sheet. I understand what is required of _____and that our participation is voluntary. I also understand that we can choose to withdraw at any point and that we can withdraw any information I have provided.

I understand that the results of this study may be published but that all identifying details will be excluded.

Parent/Legal Guardians Signature _____

Child's Full Name _____

Child's Date of Birth _____

Date _____

Appendix E. Infant Reflexes

The Developmental Pattern of Infant Reflexes Used to Assess the Neurological Development of Infant Participants

Reflex	Developmental pattern
Walking	Disappears by 8 weeks
Grasp	Disappears between 3 and 4 months
Rooting	Disappears between 3 and 6 months
Moro	Disappears by 4 months
Tonic neck	Disappears by 4 months
Babinski	Disappears between 8 and 12 months

Note: adapted from Bee, H. (2000). The Developing Child (9th ed.). MA, USA.: Allyn & Bacon Needham Heights, p. 85 and Arvedson, J. C., & Brodsky, L. (2002). Pediatric Swallowing and Feeding: Assessment and Management (2nd ed.). New York: Singular Publishing Group, p. 56.

Appendix F. Adult Participant Recruitment Poster

Would you like to participate in non-invasive brain research …while you sleep?

We are looking for healthy men and women
in two age-groups:
between 20 and 35 years and 65 years+
It will take approximately 8 hours, overnight.
Please contact Bronwen Kelly on (03) 378-6094
Or email bmk21@student.canterbury.ac.nz

This project is currently underway at
University of Canterbury Swallowing Research Laboratory
At the Van Der Veer Institute for Parkinsons and Brain Research, Christchurch
This research project has been reviewed and approved by the Canterbury Ethics Committee.

Canterbury DHB
District Health Board
Te Poari Hauora ō Waitaha

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Appendix G. Adult Participant Case History, Information Sheet, and Consent Form

Please read the following note before answering the questions below. You are invited to participate in the research project entitled: The Role of the Cerebral Cortex in the Coordination of Respiration and Swallowing in Humans by completing the following case history form. The aim of the project is to evaluate the co-ordination of swallowing and respiration during sleep and wake of healthy individuals and to compare these results to people younger and/or older than yourself. Any information that may identify you personally will not be disclosed to anyone other than the researchers involved in this study. You may choose to withdraw your participation or any information that you have provided at any time. **By completing this form, however, it will be understood that you have consented to participate in the project, and that you consent to publication of the results of the project with the understanding that anonymity will be preserved.**

The project is being supervised by Dr. Maggie-Lee Huckabee, PhD, of the Speech Language Therapy Department at the University of Canterbury (364-2987 ext 7085). She will be pleased to discuss any concerns regarding your participation in this study.

Please complete the following case history by ticking the box that is most applicable to you.

Do you suffer from the effects of any of the following medical problems:

- stroke? □
- heart attack? □
- asthma and/or any other breathing disorder? □
- Chronic Obstructive Pulmonary Disorder (COPD)? □
- swallowing difficulties? □
- severe head and/or neck injury? □
- head and/or neck surgery? □
- sleep apnoea and/or other sleep disorders? □
- neurological disorders
  (e.g., Multiple Sclerosis, Parkinson's Disease etc.)? □

- Gastroesophageal Reflux Disease (GORD/GERD)? □
- paralysis of the diaphragm? □
- Chronic Fatigue Syndrome? □
- Psychiatric disorders (e.g., anxiety, depression)? □

IMPORTANT

- **Do you have any other medical problem, which you feel may impact on your ability to participate? Yes/No (Please circle one)**

If yes, please describe……
…….

Are you taking any medications that may:

a) make you drowsy? □

b) keep you awake? □

c) affect your sleep? □

Thank you for completing this case history, we appreciate your time and assistance.

Information Sheet for Adults

You are invited to participate as a subject in the research project 'The role of the cerebral cortex in the coordination of respiration and swallowing in humans'.

The aim of this project is to compare the co-ordination of swallowing and breathing during sleep and awake and to determine whether this coordination changes as a function of age.

Your swallowing will be measured by two pieces of equipment, both of which will also be connected to the Kay Elemetrics Swallowing Workstation. The first piece of equipment is a laryngeal microphone that will be positioned over your throat and will measure the acoustics generated by your swallows. The second piece of equipment is called surface electromyography and consists of three electrodes that are positioned under your chin. It records the muscle activity of the muscles under your chin that contract when you swallow. Your breathing will be recorded by a nasal cannula, similar to those used in hospitals to give patients oxygen. It is a flexible plastic tube, which has two prongs that rest at the entrance of your nose. While you sleep, electroencephalography (EEG) electrodes will record your sleep state. Finally, a position monitor attached to an elasticized strap, fitted around your chest, which will monitor your body position while you sleep.

Your participation in this project will involve completing a case history form to provide us with any information that may exclude you from participating in this study. On acceptance into the study, you will be required to attend our research facility for approximately eight hours on one evening. There, you will be connected to a machine that will record the necessary data as you perform saliva swallows when you are awake (while lying on your stomach, back and either side, and when you are sitting upright), then while you are awake and completing a hand-held computer game task. Finally, your breathing and swallowing will be monitored when you are asleep.

Your participation will take approximately 8-12 hours of your time, overnight, on one occasion. Participation is voluntary and you have the right to withdraw from the project at any time, including withdrawal of any information that you have provided.

No subsequent participation is required in the project after this time.

There are no foreseeable risks in the performance of the tasks and application of the procedures in this study. There is no pain or discomfort associated with this procedure, however you may experience redness of the skin, associated with use of adhesive electrode patches.

Your right to privacy will be retained. Your name will not appear on the recorded data or on any published material resulting from this research project. Only those who are directly involved with the research project will have access to your recorded data.

This information sheet and consent form will remain in a locked cabinet in The Swallowing Research Laboratory.

This research project is a requirement for the Doctor of Philosophy Degree. If you have any concerns regarding your participation or would like further information please contact the project supervisor, Maggie Lee Huckabee, PhD, on (03) 366-7001 extension 7085.

This research project has been reviewed and approved by the University of Canterbury Human Ethics Committee.

Adult Consent Form

I,_____give consent to participate in this research project that investigates the coordination of breathing and swallowing during sleep and wake, conducted by Bronwen Kelly and Dr Maggie Lee Huckabee, the Department of Speech and Language Therapy, University of Canterbury, with co-supervision of Associate Professor Richard Jones, of the Canterbury District Health Board, Christchurch School of Medicine and Health Sciences, and University of Canterbury.

I consider myself fit and able to participate in this study.

I have read and understood the attached information sheet. I understand what is required of me and that participation is voluntary. I also understand that I can choose to withdraw at any point and that I can withdraw any information I have provided.

I understand that information gained form this research project may be published but that identifying details will not be featured.

Respondent's Full Name_____

Respondent's Signature_____

Respondent's Date of Birth_____

Date _____

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